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DR. A. S. WARTHIN.

VOLUME 2 JULY, 1928 NUMBER 1

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

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Issued Monthly

ANN ARBOR, MICHIGAN

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ANNALS OF INTERNAL MEDICINE

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DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the review of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

Editor

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Entered as second class matter at the Post Office, Ann Arbor, Michigan

The Cause of the Various Clinical Manifestations in Pulmonary Tuberculosis*

By F. M. Pottenger, *Monrovia, California*

ADULT tuberculosis is a chronic disease whose clinical picture usually is made up of alternating periods of quiescence and activity. The symptoms vary according to the type and the particular state of the disease at the time of consideration. There are certain symptoms which belong almost exclusively to periods of activity, others to periods of quiescence, and still others to periods of both quiescence and activity. The disappearance of the common symptoms does not indicate that healing has been accomplished, or even that the disease is quiescent.

Most symptoms of ill health are due to altered physiologic reaction, a disturbance in the reflex arc according to Mackenzie; consequently the symptom complex of any disease will vary in different patients as their individual physiologic equilibriums vary, and, in the same patient at different times, according to the particular physiologic balance or imbalance which he happens to exhibit at the time. Difference in symptomatology is also affected by differences in virulence and in the numbers of bacilli which cause different infections.

Since the character of the disease in chronic tuberculosis depends upon the specific tissue reaction, the immunity mechanism, developed by the patient, and since this in turn depends upon certain variables on the part of both the patient and the infecting microorganisms as just mentioned, the disease picture must necessarily present many different types of reaction; and variability must be the rule.

Primary Infection Versus Reinoculation

When an infection takes place as a result of bacilli making a place for themselves in the tissues of an host, the course which it takes and the nature and severity of the symptoms which it presents will differ according to whether or not it is the first time that such implantation has occurred.

If it is the first inoculation, no immediate symptoms will appear. Symptoms do not appear until the incubation period has ended with the bacilli definitely implanted in the tissues, and the host's immunizing mechanism called into play. This period varies from a few days to a few weeks according to the numbers and virulence of infecting

*Presented to the American College of Physicians, at the Annual Clinical Session, New Orleans, March 6, 1928.

bacilli and the general physiologic state of the patient. On the other hand, if it is a reinoculation, symptoms may appear almost immediately. Usually within from six to forty-eight hours after the bacilli have found lodgment in the tissues a marked reaction on the part of the host, accompanied by symptoms, takes place.

This difference in the manner in which an individual reacts to primary inoculation and reinoculation is due to the difference in defense under the two circumstances. In the former, it is the host's virgin reaction to bacilli and is practically void of inflammatory characteristics. In the latter, on the other hand, it is a specific immunizing response, a heightened reaction, brought about by the hypersensitivity of the body cells to tubercle bacilli and bacillary products which has been brought about by previous infection. This is primarily inflammatory and exudative in character.

There are certain exceptions to these reactions which must be looked upon as the usual reaction of the tissues to tubercle bacilli, that must be borne in mind. Bartel recovered living bacilli from the lymphatic glands of a guinea pig months after inoculation which had not produced tubercle. Opie (1) has shown that when latent apical lesions are present pulmonary tissue which shows no evidence of disease contains recoverable viable tubercle bacilli. Why bacilli should at times fail to be opposed by the usual tissue reactions is not clear.

Allergy

The change in response on the part of the body cells toward a reinoculation of bacilli has come to be known as "allergy." Allergy is established by the primary inoculation and may be increased by repeated subsequent inoculations, provided the numbers and virulence of the bacilli engaged in the infection are not too great for the individual's resisting power. It is greatest after the host has had several successive mild inoculations or after he has successfully withstood a severe infection. It is not only depressed by very severe infections but sometimes lowered almost to the vanishing point. It is lowered by various stresses, and particularly unfavorably influenced by such diseases as influenza, measles and scarlet fever; likewise by pregnancy. During the conditions mentioned the power of the skin to react to tuberculin lessens and sometimes disappears completely.

The severity of symptoms produced by a certain reinoculation dose of bacilli will vary according to the degree of allergy present. The more marked the allergy the greater the reaction. A strong allergic reaction indicates a stable physiologic balance on the part of the host and a defensive mechanism which should be competent to combat ordinary invasions.

The effect of the allergic reaction is manifested in several ways. First, a reaction comes on very quickly in bodies in which allergy has been established slowly in primary inoculation; second, it takes more bacilli to produce infection after allergy has been established than before; third, if a marked allergic reaction is present it

is often able to prevent implantations from taking place, or, failing this, to cause them to become abortive in character; fourth, the passage of bacilli through the tissues is retarded or prevented by the allergic reaction, hence the danger of spread of infection is lessened; and, fifth, the inflammatory reaction, unless too severe, promotes healing by stimulating the reticulum in the tissues which are the seat of tubercle infection so that it increases in amount and forms fibrous tissue. Even the severe allergic response with its exudative reaction, which is at times followed by caseation and necrosis, can not be looked upon as wholly harmful. The exudate resolves like that of a pneumonia, though taking weeks and months instead of days; and the reticulum in the walls of the air cells and in the small blood vessels increases in amount, growing inward into the air cells and replacing inflammatory products, even caseous material. And when caseation and necrosis have taken place bacilli are often cast off in numbers such as would be dangerous to the life of the host if he had not gotten rid of them. Even the exudative reaction, serious as it sometimes is, serves as a barrier to prevent the escape of bacilli into new tissues with a consequent reinoculation.

The allergic reaction is such an intimate part of clinical tuberculosis that we can not think of them apart. While allergy is primarily defensive, its manifestations at times become so injurious that its protective nature is for the time being almost completely overshadowed. Nevertheless, if one will examine advanced tuberculous lesions carefully, in which the exudative characteristics preponderate, he will note that there are two processes which go hand in hand, the one destructive, the other conservative; and, that, while caseation and destruction may predominate in the center of tuberculous masses, the formation of fibrous tissue is going on in the periphery, and even predominates in some areas.

The character of the lesion is determined, not by the presence of an exclusively destructive or an exclusively proliferative process, but by the predominance of one or the other.

While the allergic reaction is inflammatory in character, the degree of inflammation differs greatly under different circumstances. It may be so slight that it consists only of a mild hyperemia, or it may be so severe that the affected tissues are the seat of a severe serous, fibrinous, and cellular exudate as described so well by Krause (*2*).

In order to understand the various manifestations of allergy as they are met in the course of clinical tuberculosis, it is necessary to know that allergy is a property possessed by the body cells generally, that it is possessed most strongly by the cells which make up the tubercle, and that the allergic reaction, either local, focal or general, may be called out by the presence of the tubercle bacillus itself—either living or dead—or by certain products which are produced by or from bacilli.

Exudative and Proliferative, Not Different Types of Tuberculosis But Different Degrees of Allergic Reaction

From the discussion of allergy it is plain to be seen that Aschoff's exudative tuberculosis is not a distinct type but only the pathological manifestation of a severe allergic reaction in which an extensive exudation of serum, fibrin and cells takes place in the tissues. Neither is the proliferative a distinct type. It is likewise a manifestation of allergy, but of a mild degree in which only hyperemia, or hyperemia with an exudation of small amounts of serum and cells takes place. Allergy is responsible for any degree of reaction from the mildest hyperemia followed by proliferation of fixed cells to the severest exudation of serum, fibrin and cells, with resultant necrosis of tissue. The reaction is in all probability commensurate with the ability of the tissues of the host to respond to the demands made upon it by the invading bacilli. The greater the demands, unless they be so great that they overcome the patients' immunity mechanism, the greater the allergic response and the more serious the pathologic changes. Yet if we know this is primarily a picture of defense rather than destruction, even though the latter may follow, we have a different and more hopeful attitude toward these more severe phases of active tuberculosis. They are not serious unless they overcome the ability of the cells to react further in protection of the host. Exudations are acted upon by digestive enzymes and the products carried off as they are in pneumonia, and proliferation of the reticulum in the tubercles takes place producing scar. Even in serious exudative reactions, fibrosis is taking place in the periphery of the lesions and extending centralward where it may even replace necrotic tissue.

Allergic Reaction Differs at Point of Reinoculation and in Other Foci in Body

The fact that there is a difference in the allergic reaction which takes place in the focus of disease where many bacilli are producing massive doses of antigen, and in other foci which are distant from the seat of active antigen production because they are stimulated only by small doses, must be accountable for the difference in severity which is noted in the allergic reaction seen in clinical tuberculosis in different areas and at different times.

This affords the basis for two different ways in which the allergic reaction may manifest itself in the course of tuberculosis. In all cases of reinoculation the bacilli settle in tissues which are hypersensitive or allergic and which react immediately, feebly or markedly as the case may be, in an attempt to prevent implantation from taking place. In instances where the immunizing mechanism is competent permanent infection may be prevented, and even where complete protection fails the bacilli may be hemmed in and held to a localized infection.

The presence of living bacilli in any considerable numbers, whether followed by successful implantation or not, calls out a local allergic inflammatory reaction which persists over a

greater or lesser period of time, producing a definite syndrome of active disease. It does more than this, however. Certain bacillary substances escape from the foci of disease and gain access to the blood-stream, scattering throughout the body. Wherever they come in contact with unhealed foci they may call forth an allergic response, slight or severe in character, depending on conditions present, which, while similar to that at the seat of reinoculation, yet differs in certain very important features.

In the first place it is called forth by bacillary substances which have been so diluted in the blood-stream that the focal reaction called forth by them is slight compared to that at the seat of the reinoculation where the allergic producing substances are found in large quantities. As a result the reaction in the centers of the areas of reinoculation are apt to be much more severe than those produced secondarily in unhealed lesions found elsewhere in the body. This is a very important fact to be considered in judging of the seriousness of a given allergic inflammatory reaction.

In the first place, there are two processes which go on as a regular thing in tubercle at the same time—necrosis in the center and fibrosis at the periphery—both of which seem to be influenced by bacillary products, although fibrosis is found regularly and necrosis at times as a part of the tissue reaction to minute foreign bodies. The fact that particulate matter of any kind may be associated with necrosis of the central portion of the reacting tissue mass surrounding it indicates that toxins are not necessary to its production, but does not prove that they are not a factor in the necrosis of tuberculosis; on the other hand, the argument seems to point strongly to the toxins, as being the cause of the rapid necrosis in primary tubercle. Fibrosis is favored by the stimulation which affects the periphery of the tubercle. The local reticulum increases in quantity and even spreads inward into the caseous masses at times replacing the necrotic elements.

We can now understand in part the continuous interplay which takes place between bacilli and body cells during the course of clinical tuberculosis and can see that the most potent factors in determining the character of the disease following any infection are the numbers and virulence of the bacilli which cause it.

Symptoms of Pulmonary Tuberculosis

The symptomatology in any case of pulmonary tuberculosis will depend primarily upon the number of organisms engaged in the process and upon the state of resistance of the patient at the time. The greater the numbers of bacilli in any given instance the more extensive the infection and the more severe the symptoms. When the disease is markedly active there are usually present some toxic symptoms, some of a reflex nature, and one or more of the local symptoms as shown in Table I. The cause of the symptoms is the allergic inflammatory reaction and its effect in: (1) discharging toxins into the circulation, probably both bacillary and from broken

down pulmonary tissue; (2) stimulating the afferent sympathetic and vagus nerves in the lung and starting impulses centralward which end in reflex action; and, (3) causing local irritation of the tissues at the seat of the lesion.

Early Clinical Tuberculosis

Early clinical tuberculosis in the adult usually begins in one of three ways, pathologically: either as a reactivation of an old focus, or as a metastatic extension from a previous focus, or, as a new infection from without. Sometimes reactivation in previously existing foci comes on quite suddenly as for example following acute respiratory disease such as influenza, pneumonia or bronchitis; but it also may come on slowly after severe stresses of a physical, nervous or emotional nature.

Table I

Etiological Classification of Symptoms of Pulmonary Tuberculosis

Group I symptoms due to toxemia and other causes acting generally	Group II symptoms due to reflex cause	Group III symptoms due to the tuberculosis process per se
Malaise	Hoarseness	Frequent and protracted colds (tuberculous bronchitis)
Lack of endurance	Tickling in larnyx	
Loss of strength	Cough	Spitting of blood
Nerve instability	Digestive disturbances (hypermotility and hypersecretion) which may result in loss of weight	Pleurisy (tuberculosis of pleura)
Digestive disturbances (hypomotility and hyposecretion)		Sputum
Metabolic disturbances resulting in loss of weight	Circulatory disturbances Chest and shoulder pains	
Increased pulse rate	Flushing of face	
Night sweats	Spasm of muscles of shoulder girdle	
Temperature	Diminished motion of affected side.	
Blood changes		

We may best be able to illustrate the relationship between the reinoculations which take place in clinical pulmonary tuberculosis and the allergic reaction called forth by them, and its influence in the production of symptoms, by analyzing a few chosen cases representing different phases of clinical activity.

The plate shown in Fig. 1 is illustrative of early clinical activity in which metastases took place from a previous focus. The patient, Miss E. K., was examined June 17, 1927. One month preceding examination patient had what she thought was a cold followed by fatigue, loss of weight (5 or 6 lbs.) and general feeling of low vigor. Symptoms disappeared in a few days and she regained, but on June 16 spat up one or two drams of bright blood. Physical examination revealed an active lesion at right apex, where there was roughened breathing with few râles.

This reaction probably meant the breaking down of the fibrous wall which confined viable bacilli; the escape of bacilli to new tissue; the establishment of new foci, and an allergic reaction which resulted in recognizable symptoms and signs on physical examination, and which showed as an exudative reaction in the x-ray film.

This patient had been examined by me two years previously, at which time there was evidence of an old lesion at the right apex, with no activity.

The temperature curve of this patient remained normal, after she was put at rest, during the entire course of her disease. No subsequent reinoculation sufficiently large to produce symptoms took place after the early metastases and the hemoptysis of June 16. The infiltration in the lung gradually disappeared; the signs on physical examination decreased and the exudative process in the film gave way to fibrosis. This case illustrates the dependence of symptoms on the allergic reaction produced by reinoculation and shows, how, when that has disappeared, the early symptoms may soon pass away and leave the patient in a state of false security. Had this patient not heeded this early warning but kept on working, the chances are at least even that the infection would have progressed.

Advanced Clinical Tuberculosis

Tuberculosis advances by forming metastases. No patient ever dies of his original infection unless it be such as a miliary spread or a meningeal invasion. It is only when repeated reinoculations, caused by many bacilli, have taken place, and the destructive reactions have predominated over the proliferative that death ensues.

Sometimes repeated reinoculations will take place before a real destructive disease is established. Even widespread exudative lesions are not inconsistent with healing.

Mrs. E. J. illustrates this fact. She entered the sanatorium Nov. 23, 1925, with the following history. Poor health for two years. Main symptom, indigestion. In June of 1925 severe "cold" followed by fatigue, loss of voice, loss of strength and weight (7 lbs.), cough and expectoration. In August, left-sided pleurisy and flushing of the face each evening. Had previously had several periods of elevation of temperature. At time of entering sanatorium, temperature was between 99 and 100°, but under rest came to normal within first month and remained so for the most part until healing was completed. The signs of activity gradually disappeared. The toxic symptoms disappeared first; the reflex symptoms remained longer, some until healing was complete.

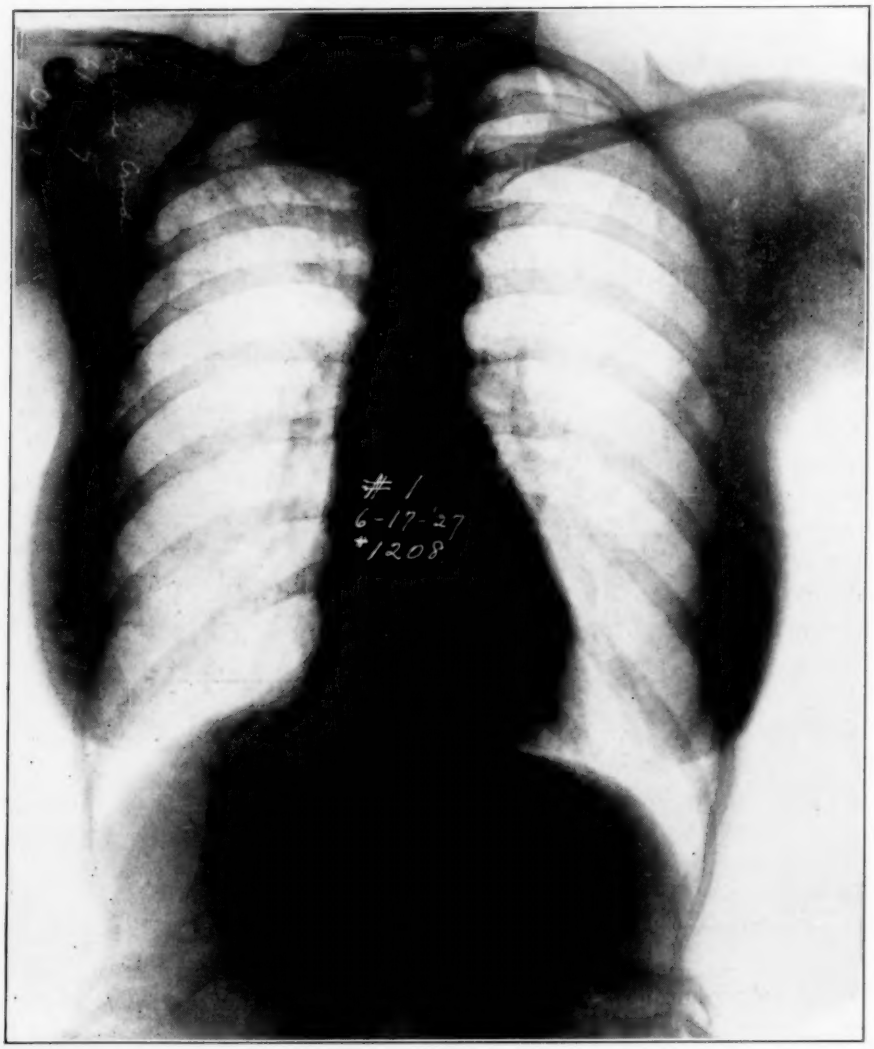

FIG. 1. Illustrating an early clinical activity in which metastasis took place from a previous focus. The allergic reaction which took place at the time of the metastasis one month before has disappeared.

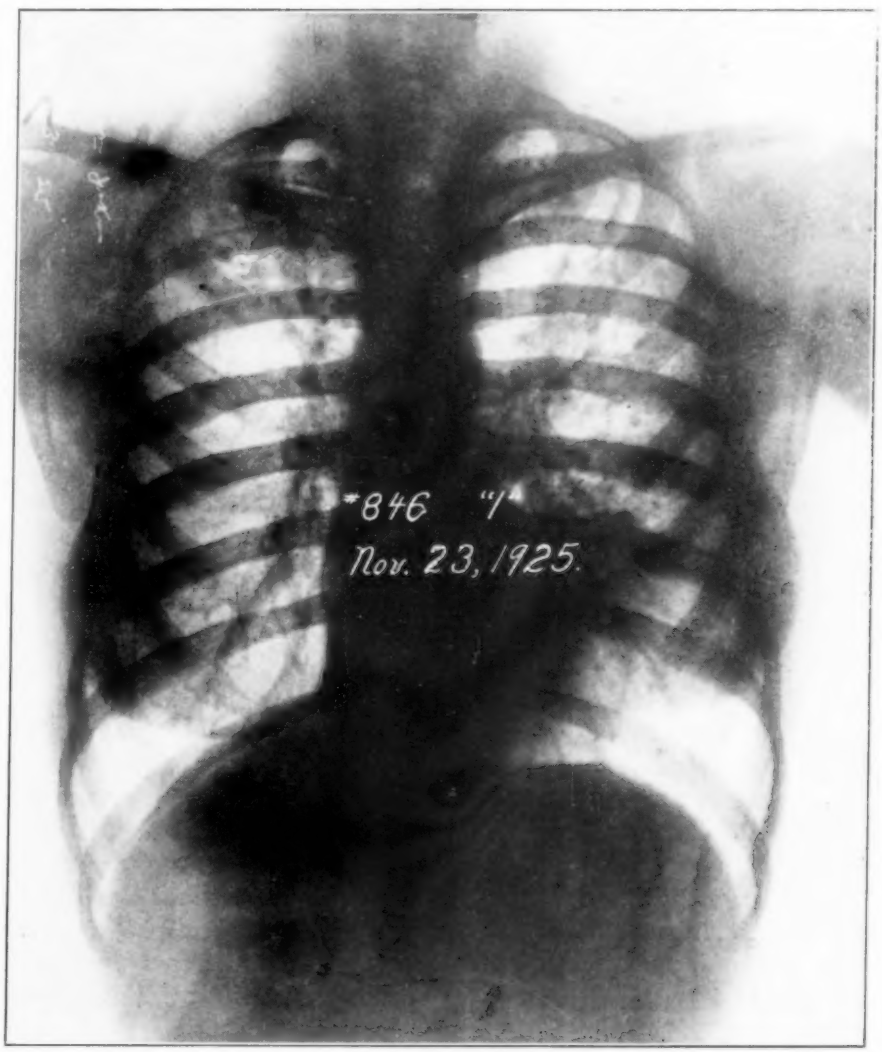

FIG. 2. Widespread allergic so-called exudative type of Aschoff, with little loss of tissue.

The plate in Fig. 2 shows a widespread exudative lesion with little loss of tissue. The plate in Fig. 3, taken two years later, shows how such a lesion, when not followed by repeated large reinoculations, may go on to absorption of the exudate and healing. The healing in this case was brought about in part by resolution, the exudate resolving the same as in pneumonia, only taking months instead of weeks for the accomplishment; in part by the formation of fibrous tissue, and in part by calcification, as is seen in both apices.

Sometimes a process becomes very acute from the beginning. This is illustrated by the following history. Mr. G. L. B. was examined on Jan. 5, 1924, at which time he was recovering from influenza. Chest showed slight evidence of old tuberculous process at both apices, without activity. X-ray revealed a calcified node on a level with the first rib, posteriorly; also few calcified nodes in hilum; no active tuberculosis, as shown in Fig. 4.

Patient again presented for examination Nov. 8, 1927, giving a history of feeling ill during preceding few weeks, with languor, rise of temperature to 103°, loss of weight, severe cough, and free expectoration (20 cc in 24 hours, with 25 bacilli per field).

Physical examination showed cavity at left apex and considerable infiltration throughout the upper lobe, with numerous moist râles. The X-ray plate, Fig. 5, shows that the calcified node seen in Fig. 4 had been replaced by a cavity, and that a marked spreading had taken place throughout the entire upper lobe. Such a rapid spread, taking place before a competent immunity has been established furnishes the condition for a rapidly fatal tuberculosis.

After the disease is once well established its course may be either progressive or regressive. Which the course shall be, is determined by the frequency with which bacilli escape from existing foci, their numbers and virulence and the degree of competence of the immunizing mechanism at the time the spread takes place. Competency in this connection is only a relative term. What would be competent for the withstanding of one reinoculation would not be for another.

We assume that in case of advanced progressive tuberculosis there is always an unprotected front from which bacilli sally forth more or less constantly. The more extensive the areas of activity the greater the opportunity for them to escape in large numbers. When they escape they call out an allergic reaction which, if severe, is not only inflammatory but exudative in type. This acts as a barrier to their further escape and so proves to be one of the chief methods of defense against a more extensive bacillary invasion. So while exudative lesions are correctly interpreted as being signs of activity, they are also very important barriers of defense for the organism against further bacillary spread.

Miss D. S. had been suffering from chronic tuberculosis for a period of several months. Had had repeated periods of high temperature (101 and 102°) for two or three weeks at a time, then dropping down to nearly normal at which time she would re-

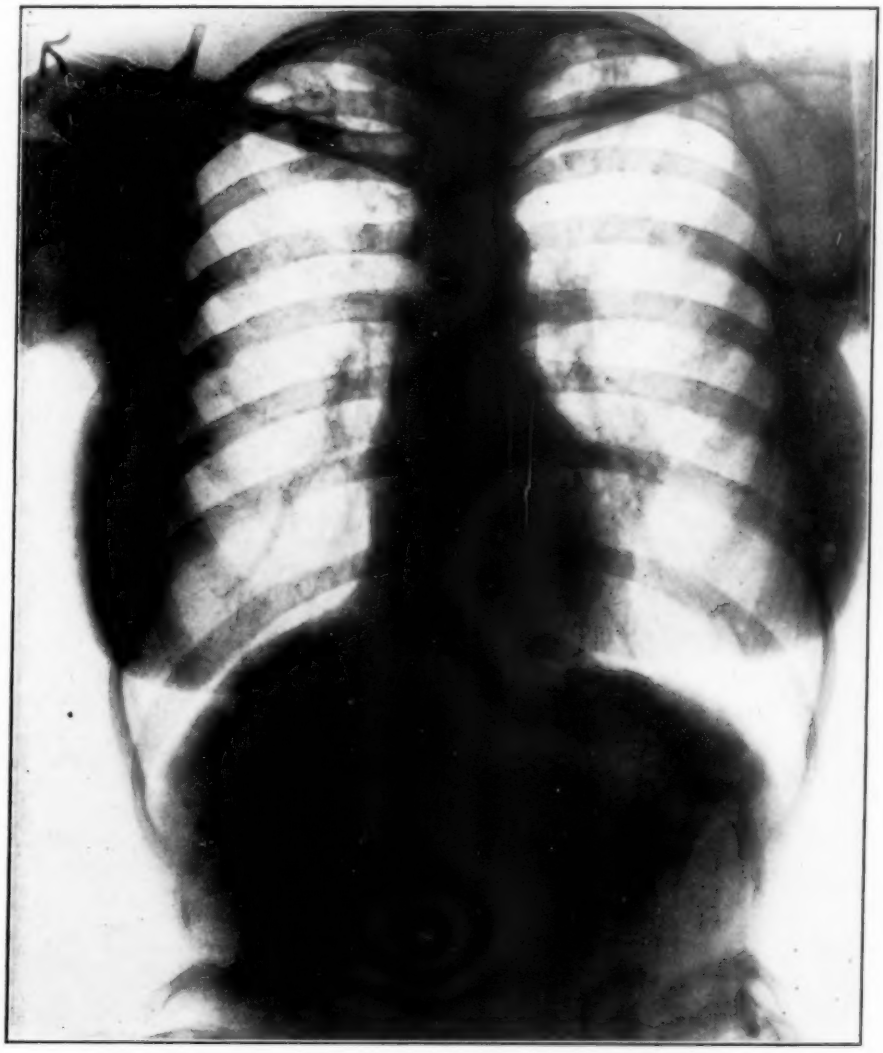

FIG. 3. Same chest as shown in Fig. 2, taken two years later. The exudation has disappeared, healing having taken place largely by resolution.

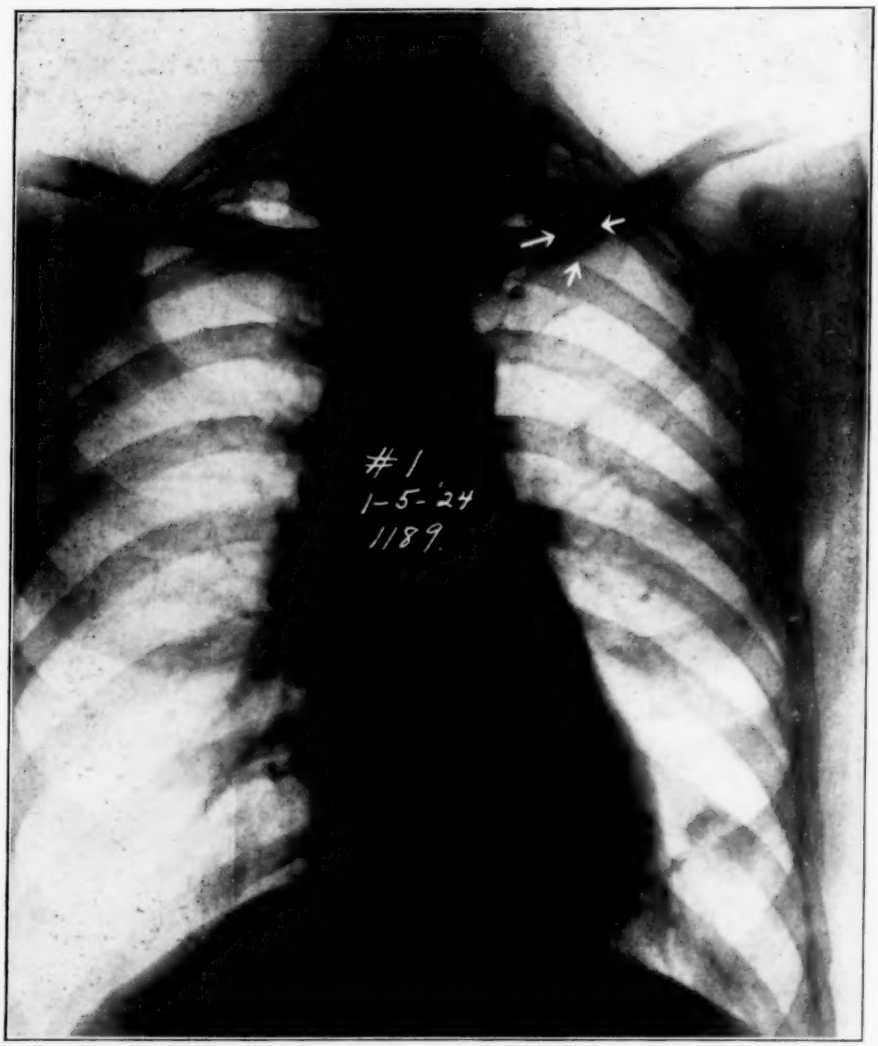

FIG. 4. Plate of a chest showing calcified nodule in the upper portion of the left lung.

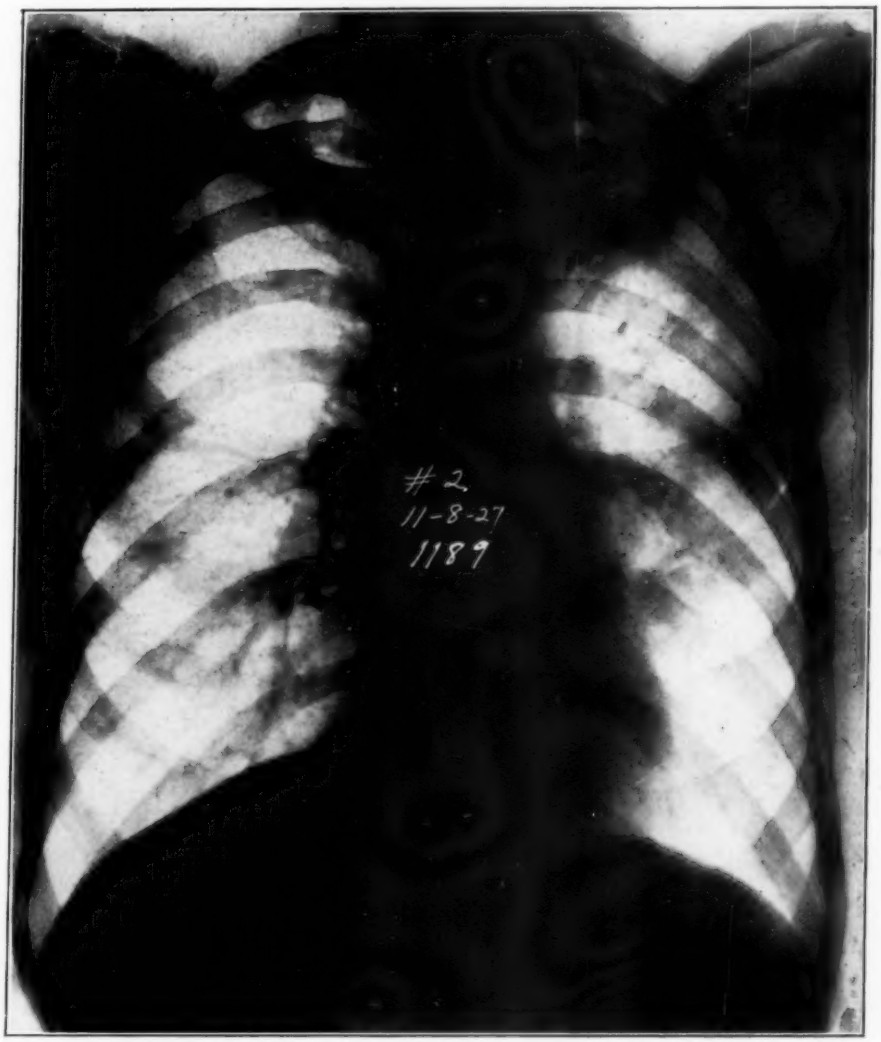

FIG. 5. Same chest four years later. Reactivation in area surrounding the calcifdie node, with cavity formation and general spread to neighboring tissue.

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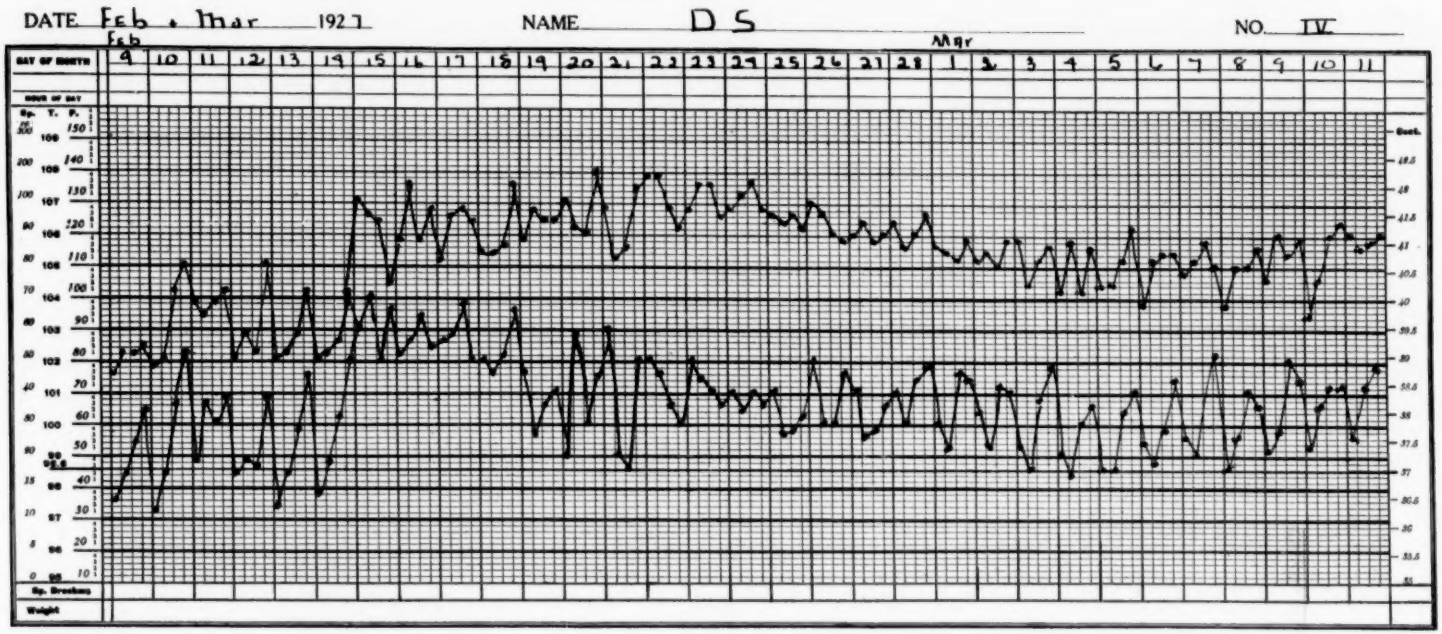
TEMPERATURE CHART


DATE Feb. - Mar 1927
NAME D S
NO. IV
Feb
Mar
DAY OF MONTH
9 10 11 12 13 19 15 16 17 18 19 20 21 22 23 29 25 26 21 28 1 2 3 4 5 6 7 8 9 10 11
HOUR OF DAY
Sp. T. P.
Sp. Breakage
Weight

Sp.—Sputum.

FIG. 6. Chart showing the effect of severe allergic reaction upon the temperature and pulse. A reinoculation on February 9 was followed by a second on the 15th, before the effect of the previous one had disappeared.

cover much lost ground. On Feb. 9, a moderate reinoculation took place, and on the 15th, before the effects of this one had disappeared, a second very severe reinoculation occurred, as shown in the chart, Fig. 6. As a result of these reinoculations a severe allergic reaction of the exudative type took place. Auscultation showed many râles throughout the entire right and part of the left lung. The patient's temperature ranged from 102 to 104° for one week and then remained in the neighborhood of 102° for a month. The patient was severely toxic; appetite failed; lost weight; cough was severe; sputum increased from 40 cc in 24 hours Feb. 1, to 140 cc in 24 hours, Mar. 14.

Patient was considered dangerously ill, but began to improve. Temperature gradually lowered, appetite improved, weight increased, and cough and sputum lessened, all of which indicated that her immunity had greatly increased as a result of the reinoculations and that the allergic reaction was passing off. This was followed by other similar reinoculations over a period of nearly a year, when finally immunity was so well established and the bacilli were so well incarcerated that the disease reached a stage of inactivity. The temperature dropped to normal, all symptoms of toxemia disappeared, the patient gained ten pounds in weight and assumed a state of general well being.

At times patients have one or two severe reinoculations with very marked allergic reactions, which result in sufficient stimulation of their immunity mechanism to cause the disease to go on to complete healing. This is in line with what we have seen in the use of tuberculin. Now and then we have seen healing of early lesions follow a severe tuberculin reaction. von Hippel (3) reports several cases of tuberculosis of the eye which went on to healing after severe inflammatory reactions following injections of tuberculin.

The following case shows how the course of an active gradually spreading pulmonary tuberculosis was brought to a standstill by one severe reaction following a large reinoculation. The course of the disease was turned from one steadily advancing to one gradually receding.

Miss E. S., 18 years of age, examined September 1, 1927. History. Father, mother and one sister died of tuberculosis. Patient three years old when father died, and eight when mother died. Intimate association but not continuous. Measles, whooping cough, bronchitis during fifth year. During past ten years occasional twinges of left-sided pleurisy. September 1926, strength and endurance declined. Fatigue, poor appetite, loss of weight (8 lbs), rise of temperature to 99 and 100°. January 1927, severe left-sided pleurisy for one week. August 1927, severe pleurisy with slight cough. Had gained in weight from January until August, but lost five pounds during August.

Examined by me on Sept. 1, 1927. Symptoms: fatigue, loss of strength and endurance, decreased appetite, loss of weight, temperature 100°, severe cough, slight expectoration, 8 cc of

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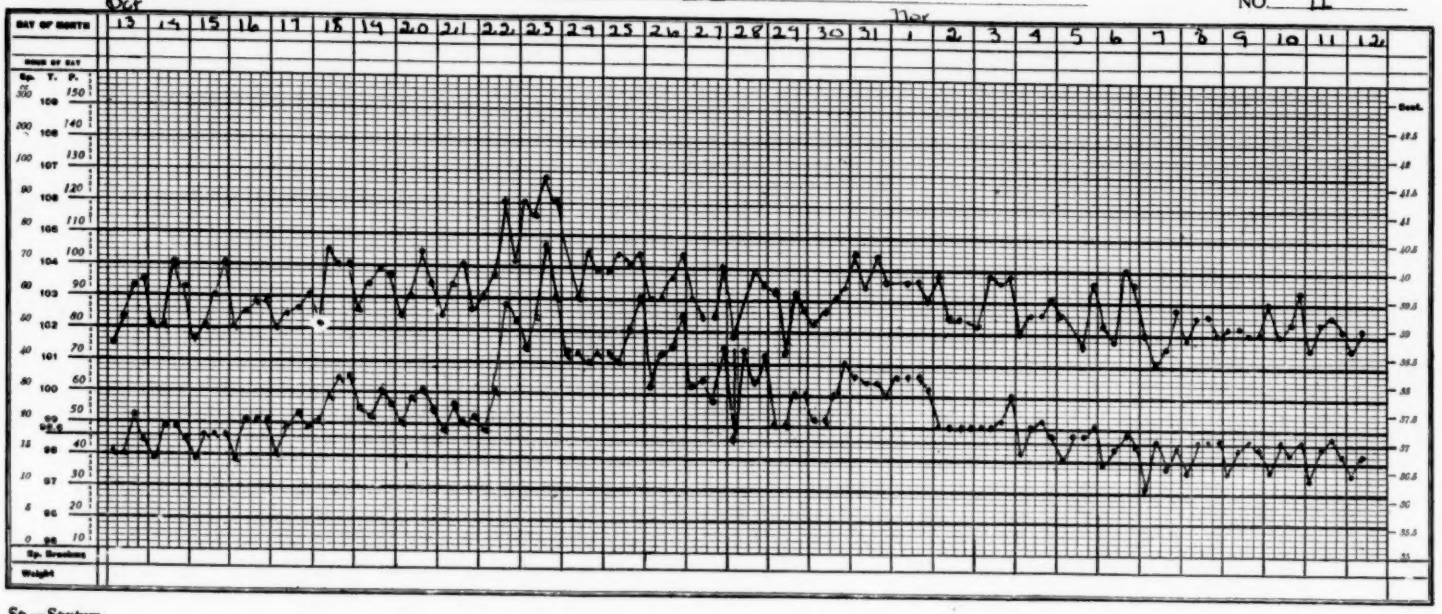
TEMPERATURE CHART

DATE Oct and Nov 1927 NAME E S NO. II



Sp.—Sputum.

FIG. 7. Clinical chart showing the effects of a very severe reinoculation upon the temperature and pulse, followed by normal temperature. This one severe reaction raised the patient's immunity and hastened recovery, and was followed by healing of an extensive infiltration throughout the left lung and in the upper portion of the right.

sputum in 24 hours, with 10 bacilli per field.

Physical examination. Left lung: Extensive tuberculosis through upper lobe; much scarring, but also much activity. Pleurisy at the base. Right lung: Same condition but less extensive.

Under rest patient's temperature came to normal in about one week. Remained so for about a month. On October 18 a reinoculation took place, causing a severe allergic reaction. The temperature was 100.5°; on the 22d, 103°, and on the 23d, 104.7°. It gradually declined, reaching normal November 17. Patient was severely ill. Much aching, extreme pleural pain over left side, lack of appetite, insomnia and rapid loss of weight. Marked increase of cough and expectoration, reaching 30 cc in 24 hours on October 22, and a much greater amount, although not recorded, a few days later. The clinical chart showing the effects of this severe reinoculation is shown in Fig. 7.

Physical examination at this time showed marked increase in moisture throughout the left upper lobe, indicative of a severe allergic reaction, exudative in character, with a lesser reaction in the right upper lobe. Following this, patient's temperature came to normal and remained so until present time (Feb. 10, 1928). Has gained 18½ lbs. in weight; appetite excellent; cough practically nil; sputum 10 cc in 3 days, with 3 bacilli per field.

Physical examination in February reveals very marked reduction in physical signs in both lungs; right side entirely free from râles. As a result of the severe reinoculations that took place on October 18 and 22, the patient developed sufficient immunity, and sufficient allergic reaction took place throughout the areas of infection to cause a marked increase in fibrosis in and about the tubercles with a very definite stimulation to healing. It is possible that this one severe reinoculation may be ample to not only bring the disease to a state of quiescence but to carry it on to healing.

The escape of a few bacilli probably rarely causes new implantation unless the immune forces of the host are greatly depressed. On the other hand, if we may draw conclusions from experimental studies, these small reinoculations serve two very important purposes, that of stimulating the specific immunity reactions and raising them to a higher level, and that of calling forth slight allergic reactions in the periphery of tubercle and hastening fibrosis and healing.

Fig. 7 is a temperature chart representing a small reinoculation, yet one of sufficient magnitude to call forth definite symptoms. The symptoms were similar to those produced by a tuberculin reaction, viz.: malaise, aching, loss of appetite and weight, constipation, increased cough and expectoration. The picture was that of an allergic reaction of moderate degree. It is rational to assume that the focus from which the bacilli which called forth this reaction escaped might readily have shed others, yet rarely in this particular type of the disease do we find one reaction superimposed immediately on a previous one. They are usually weeks—sometimes months—

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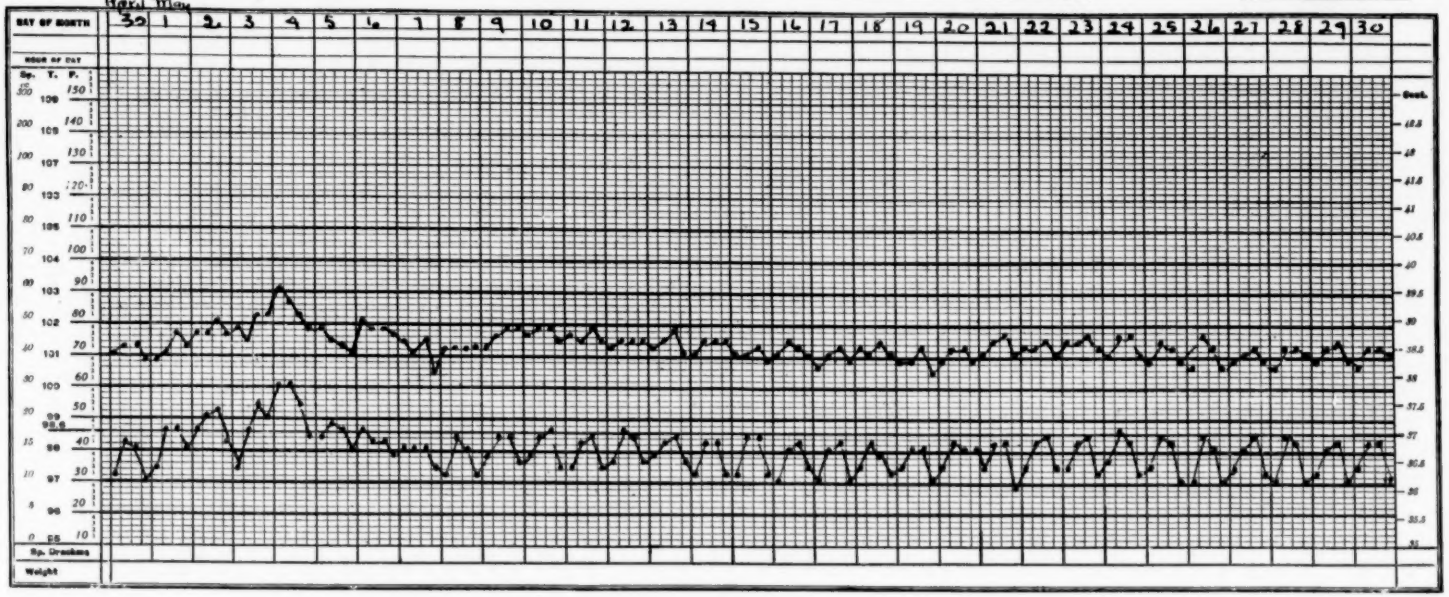
TEMPERATURE CHART

DATE April + May 1921 NAME L P NO. III



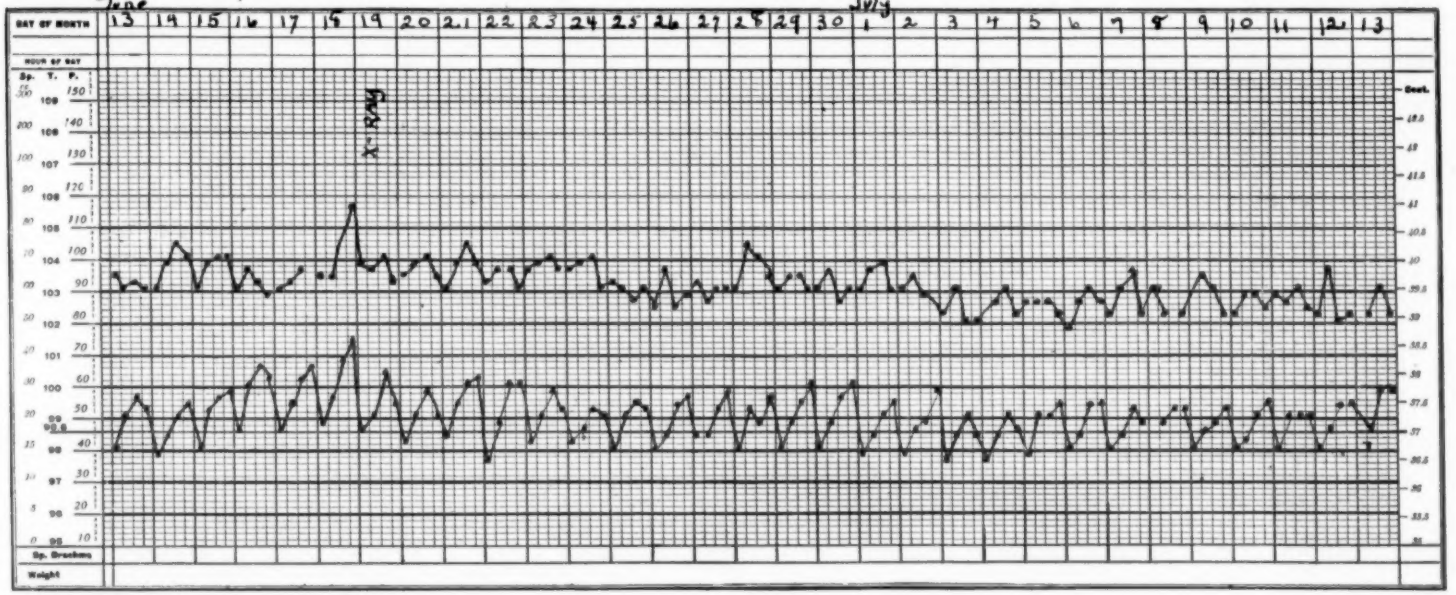
Sp.—Sputum.

FIG. 8. Chart showing a normal temperature curve broken by a slight elevation of a few days' duration, accompanied by increased cough and expectoration, malaise, headache, loss of appetite. Reinoculation caused by moderate numbers of bacilli.

POTTENGER SANATORIUM FOR DISEASES OF LUNGS AND THROAT
MONROVIA, CAL.

TEMPERATURE CHART

DATE June + July 1927 NAME D. S. NO. VIII



Sp.—Sputum.

FIG. 9. Chart showing slight but continuous rise of temperature, which had followed several severe reinoculations. Temperature due to the absorption of toxins caused by destruction of both pulmonary tissue and tubercle bacilli.

apart. Probably a few bacilli escape more or less continuously in many or most cases of this kind, yet not in sufficient quantities to call out continuous toxic reaction. Reflex action, however, is usually present in some organs.

At times we see a moderate reaction from reinoculation which fails to pass off short of two or three weeks, as shown in Fig. 8. Such temperatures are accompanied by slight toxic symptoms and could well be due to repeated reinoculations, insufficient to produce decided reaction of themselves, yet sufficient to prevent the passing off of the allergic reaction caused by the first reinoculation. It seems to me more probable, however, that they are due to the continuous absorption of toxins, the product of destroyed pulmonary tissue, in small amounts.

Large reinoculations at times cause a more or less abrupt rise of temperature, although as a rule the maximum temperature is not attained until several days after the reaction has begun. Such reactions are accompanied by severe symptoms and more or less prostration of the patient. The lung, which before, may have been only the seat of a mild process, at once takes upon itself a severe exudative inflammatory reaction. Such symptoms are prolonged often for weeks and even for months. Reinoculations continue to take place; bacilli are destroyed, tuberculoprotein enters the circulation, which, together with the products of the exudative reaction and the broken down pulmonary tissue, keep up a prolonged and often very injurious toxic action on the patient. If the patient withstands such a process, it is by developing a high grade of immunity and an unusual ability to withstand the effects of the toxins.

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Factors in the Pathogenesis of Tuberculosis*†

With a Preliminary Discussion of Activity

By Allen K. Krause, *Baltimore*

THIS address starts with the premise that the term *Pathogenesis*, applied to tuberculosis, seeks to define a purely clinical concept. Modern medicine has made it plain that anatomical effects of tubercle bacilli quite commonly and, indeed, rather characteristically exist in the body without appreciable disturbance of the economy of the human organism. After bacilli are received, tuberculous foci form; they evolve and subside, they come and go, they reproduce and spread, they remain engrafted throughout a lifetime; meanwhile, if situated away from the surface of the body, they pursue their course entirely unknown to their possessor, and unfelt. If (let us imagine) they do affect function, the exaltation or depression is not marked enough to transgress physiological limits; for it is not noticeable by the host and not to be measured as abnormal by the observer. Quite likely the vast majority of all tuberculous formations are, in our day and in our civilization, of this type. For the possessor they are, as it turns out, as though they had never been; yet, again for the possessor, they represent the potential seeds of untold trouble,—of disease and disability and death.

All this has become so well understood that efforts almost innumerable have been made to wring from the patient and the work-bench the secrets of what we may call the *genius* of tuberculous infection. Not a few writers have proceeded upon the assumption that in and after the act of tuberculous infection there must be at work some dominant influence or influences that will determine the course an infection is to take. Some have looked for effective or decisive attributes of parasite; others for moulding or governing properties within the host. Or, despairing of this line of inquiry, still others would be content if only they could recognize and become familiar with the earmarks of tuberculous infection which is in essence deranging and disabling as against that which will go its way unheralded and unseen. We medical men are no exception to the run of mankind in our ardent eagerness for a sign; and some of us have professed to see the signs of "good" versus "evil" tuberculous infection; sometimes in the structure of

*From the Kenneth Dows Tuberculosis Research Fund of the Johns Hopkins University and Hospital, Baltimore, Maryland.

†Presented in part at the annual meeting of the College of American Physicians, New Orleans, Louisiana, March 6, 1928.

the tuberculous process itself, as we have visualized its image out of the evidences of auscultation or out of its shadow on the roentgen-film; sometimes in the vigor and extent of the specific reaction of allergic tissues; or in the behavior of the blood-serum subjected to one or another of several tests.

However, here in tuberculosis also, as in every other one of its realms, Medicine, it will not be unfair to state, remains in practice the art it always will be and must be whenever it deals with the patient. The data that will betray the character of a human being's tuberculous infection are not to be found apart from the patient; and appraisal will approach accuracy only as the whole man passes under observation. Not from a one or a four-plus reaction, not from a fainter or brighter red, not from a dearth or shower of stethoscopic noises, not from a screen or film conveying merely the shadowed densities of the morbid process, not even from the tuberculous focus itself brought to light at autopsy or biopsy, may the effects of a tuberculosis be estimated,—the effects, past, present and prospective, in those cases in which interpretation and decision can be of most value. Up to a certain point, a point that is usually well along in the history of an infection, it is the effect upon the man, far more than, say, upon the lung, that will count in leading us to an opinion as to what his now-discovered foci of tubercle mean and have meant to him, and therefore what they probably will mean to him.

For it is only as a person is disturbed by tubercle that he has tuberculosis that is pathogenic, that is, originating illness. We might, if we wished, give the term a quite limited significance, and restrict its use to the *first* dawning of noticeable dysfunction or illness in any particular case. But the natural history of tuberculosis proclaims that clinically it is a notoriously relapsing disease. In its earlier phases a fair proportion of victims enjoy even years of complete freedom from illness, during which they possess unimpaired function and capacity for work. When some of these again break down, as often happens, they enter a new era of pathogenesis; and there is no reason to believe that this pathogenesis of relapse or exacerbation is conditioned by factors that categorically are unique, and different from those that lead to first pathogenesis. There may be differences of quantity, but surely there are none of kind or quality.

Discussion of Activity

In a way *Pathogenesis* is synonymous with *Activity* in any discussion of tuberculosis. However, the present relation does not conceive of the two terms as meaning exactly the same thing. If, broadly, *Active Tuberculosis* refers to any and every state of tuberculous infection that is giving rise to manifest functional signs of its presence, then *Pathogenesis* may be used to denote the transition from a state of entirely unfelt infection to one of activity,—of everything connected with this act of transition as well as the period of transition itself. *Activity* may comprehend a shorter or longer period in the course of an infection, from a quite transitory episode to one prolonged uninterruptedly through

years. Pathogenesis has to do with the awakening of activity, whether this is setting in for the first time or is being repeated in the individual case. Accordingly, in any discussion of pathogenesis we must keep clearly before us what we are to understand by *Activity*.

Any definition of *Activity* will be moulded by the purpose of the user of the term. For instance, every student of tuberculosis recognizes that tuberculous processes evolve along a line or cycle of anatomical changes that represent a more or less step-like progression of *possibilities* of increasing gravity or seriousness so far as the infected organ and body are concerned.

In other words, if observed to develop in a rather characteristic way, a process is conceived of, and rightly so, as "advancing." In a similar manner, tuberculous formations may give out signs of retrogression, and thus engender ideas of anatomical arrest, or scarring, or healing. Either anatomical progression or retrogression may, on occasion, be predicated from physical signs or X-ray appearances, altogether independently of the functional capacity of the patient. Indeed, the impression gained from the anatomical status or course may, not infrequently, be at variance with that based upon the patient's functional (clinical) condition at the time.

Increasingly refined methods of physical exploration have made it possible to reconstruct visually the underlying structure of tuberculous processes with constantly improving fulness and accuracy. It is no wonder therefore that this circumstance has tempted not a few phthisiologists to determine the clinical status of cases, and to predict their course, from anatomical particulars. Hence the term *Pathological Activity* which has been coming into usage. Fettered by the more rigid requirements of purely functional or clinical concepts of activity, a number of writers have maintained that in tuberculous infection there is an activity expressed by purely pathologico-anatomical changes, at least for a time, which may be estimated and used decisively in both diagnosis and prognosis.

The contention is undoubtedly based upon an element, a modicum, of truth. If, too, a closer attention to anatomical particulars could give us, without immoderate error, a satisfactory estimate of what a fair proportion of tuberculous infections were about to do to the patients concerned; if, say, in the absence of clinical manifestations, it could with fair accuracy select asymptomatic patients for treatment; if, in other words, it could really anticipate with some precision the onset of the functional derangements of tuberculosis, the employment of so-called pathological activity as a guide in diagnosis could be nothing else than praiseworthy.

For it will be conceded that anatomical changes must precede any functional disturbance to which they give rise, and the main effort of diagnosis in tuberculosis has ever, in modern days, been directed to pushing diagnosis farther and farther back into the history of the individual infection. Even in this era of a perfected sanatorium regimen and collapse therapy it remains as true as ever it was that the chances of ultimate cure of tu-

berculosis improve immeasurably as treatment is instituted early rather than later.

We can imagine certain anatomical changes, or, better, *ensembles* of changes, that are so definite, so marked, and so characteristic that of themselves they can hardly mean tuberculosis in any other state than active clinically. But it is certain that such instances become more than probabilities as to status only as the disease concerned enters the more advanced stages, when too it will be documented as active by less equivocal evidence. There are exceptions to the general proposition; but by and large it is in the case of the earlier tuberculous processes, anatomically speaking, where something besides symptomatic evidence of activity, and antedating the latter, could be of greatest service in diagnosis, if only it would work and with some precision select patients for treatment. It is certain that the data of pathological structure will not supply the desired information. There is no known type of anatomical changes, except complete fibrosis, or combination of changes, which has anything intrinsic to assure activity or inactivity of focus. Under the proper circumstances practically every one of them can lead to symptoms, that is, activity, just as practically every one can exist without symptoms. The "proper circumstances" are, so far as we know, influences outside the foci and acting through the body and the organ involved. Then, as we shall see, when these influences are brought into play, foci hitherto inactive, or temporarily so, become active,—even precipitately sometimes and under conditions that will allow no opinion of focal structure acting as the decisive influence. In other words, pathogenesis has taken place, as foci remained unaltered, but as bodily activity underwent changes.

In this connection we may set down the fruit of an enormous clinical experience, with which we agree. It is Friedrich von Müller writing (1):

> We know that fibroid scar-tissue is the result of a proliferative process, and we know that a fresh inflammatory infiltration usually represents the more exudative pneumonic character, but we cannot foresee whether an infiltration will turn to necrosis, caseation and destruction, or whether proliferative processes will prevail and lead to the formation of connective-tissue and scars. . . . Even an acute and rather extended pneumonic exudative infiltration does not necessarily turn to caseation and the formation of cavities, but not seldom it runs a benign course, diminishes in size and leaves a net-work of fine fibrous bands. The differentiation between exudative and proliferative tuberculosis is an expression of the momentary anatomical state, but not of the issue of the disease and the fate of the patient.

von Müller was speaking of prognosis and of diagnosis, of the course of tuberculosis in cases in which illness is definite and well marked. He introduced the above remarks with the statement that "the modern distinction between exudative and proliferative tuberculosis is only of anatomical but not of clinical importance for the doctor." If the opinion is sound as concerns well-defined disease, how much more forcibly can it be applied to earlier and more obscure and equivocal cases, in which, in general, both anatomical and functional evidence of the infection will be less plainly expressed!

One need have no quarrel with the term *Pathological Activity* provided it is applied correctly. Kept in its place, and used there, it can be of service. In the case under treatment, for instance, definite anatomical alterations, for worse or for better, suggesting impending tendencies toward failure or improvement of the patient during a period when symptoms remain stationary, may conceivably lead us to modify treatment to the advantage of the patient. But, in the present state of our information, *Pathological Activity*, if used widely in diagnosis, and especially first diagnosis, would, by and large, be likely to result in egregious error.

For, after all, if we ask ourselves why we bother at all with the question of activity in tuberculosis, we find that it is for the purpose of arriving at a *practical* diagnosis. The detection of a condition of tuberculous infection has been shorn of all difficulty and most of its doubt. But experience and common sense have taught us that tuberculous infection, of itself, need not be and usually is not of significance. For practical purposes a diagnosis of tuberculosis aims at the detection of tuberculous infection with a difference, the difference consisting in manifestations that render the subject a fit case for treatment. Obviously, we cannot commit all the infected to treatment; nor would we gain anything if we could. Where then draw the line?

We might arbitrarily settle upon any one or a combination of standards. We might, for instance, hit upon a certain measured vigor of skin reactivity to tuberculin as the line beyond which no tuberculous person should go untreated. Something like this has been suggested; but it is common clinical experience to find every intensity and degree of cutaneous allergy, even the greatest, existing in many people of every age who are in perfect health and who later do not fall ill with tuberculosis; while at the same time persons with but a trace of reactivity are not rarely found to be down with the disease at the time the test is given, or come down with it shortly afterward.

We find a not dissimilar set of conditions limiting the usefulness of serological tests when these are called upon to carry the load in determining activity. And only a limited experience should suffice to convince the unprejudiced observer that any anatomical standards would likewise fall far short. They would undoubtedly commit to treatment numbers of persons who would not fall ill if let alone, while their absence would be found to be a sorry and treacherous warrant that illness was not present or impending.

In any appraisal of the state of a tuberculous infection we, as medical men, must again be mindful of the purpose at hand. For special purposes there may be estimates that are to be based on somewhat special considerations. To come upon the anatomical marks of the infection in a recruit for the army or a candidate for disability or life insurance introduces standards of interpretation that may differ from those applied to the subject in ordinary life. An army career postulates exposure to undue hardships, and the effect of undue hardships upon existing tubercle postulates likelihood of activation; at the same time a soldier

invalided by tuberculosis is only too likely to become a years-long pensioner of the Government. Similarly, candidates for disability or life insurances are selected according to scales of comparative risks, and anatomical tubercle of a certain kind and extent may detract from full or required expectancy, no matter how inert the foci may be or may have been. We may therefore in such special instances arrive at a diagnosis of significant tuberculosis,—signifiicant in view of the particular conditions that are to be fulfilled.

But in medical practice we face a problem that calls for a practical diagnosis, in performing which we aim to satisfy what in the circumstances will be best for the patient, his family and society. In furtherance of this it must be plain that a subject's past and present ability or inability to live a customary normal existence must be our guide. It is now lapse of capacity that spells activity of infection, and calls for action,—in this case the prompt institution of treatment. The clinical or symptomatic gauge or standard of activity is not perfect. It will have its exceptions, and now and again, if adhered to too rigidly, its tragedies. But we submit that we have no better standard, and that, as a working rule, it will result in fewest mistakes and pitfalls for the practitioner. It involves moreover relatively simple concepts, to be arrived at by the simplest of means. All that is necessary is the determination of three elements. *These are the anatomical manifestations of tuberculous infection, the presence of symptoms, and the assurance that the symptoms are due to the infection.* Given these, there is active tuberculosis. Let one feature be lacking, and either the infection is not active or a tuberculous infection cannot be proved to exist.

However, the case for activity is not yet complete. In any determination of activity, one condition more remains to be satisfied before the individual patient's status can be settled.

This is the patient's tolerance of stress. If a man with anatomical tuberculosis complains of any of the well-known symptoms that can be correlated with his infection, or if these symptoms are apparent to the examiner, it is enough: he has active tuberculosis. *But if a man with foci of tubercle alleges that he is entirely free from symptoms and if he exhibits none, it is not enough: he must be put to some kind of a functional test.*

Such a test may comprise any convenient form of overactivity, and usually of a physical nature, when the effects should be carefully observed. Complaints or objective evidences of symptoms now become significant. Chief of these is fatigability, or lack of endurance, or abnormal tardiness in recovering from fatigue; important is abnormal height or depression or range of temperature, or cardiovascular or digestive irritability and instability, or onset or accession of cough or expectoration. If such symptoms make their appearance in the circumstances, it means almost inevitably that the patient has in truth been having symptoms, no doubt slight, notwithstanding his denial. It surely means that the balance between his foci and his organism is being so delicately maintained that it can be easily upset, and

that toward the side of appreciable activity. His case may accordingly be classed as active.

We would therefore designate as active any and every case of tuberculous infection in which symptoms are occurring spontaneously or in which they can be elicited, and in which such symptoms result from the presence and activities of the tuberculous processes.

Before leaving this lengthy preliminary discourse on *activity* it is desirable, and perhaps necessary, to refer to one important consideration on which we should think straight in any and every application of the term. Briefly it is this: *That any and every symptomatic evidence of dysfunction due to tuberculosis means activity of the disease: that the slightest symptom lifts a case out of the category of latent, or quiescent, or inactive tuberculosis, and is enough to make it active: that for as long as the slightest symptom exists or can be elicited a case must be considered as active.*

The puny, the stunted, the lackadaisical child has really active tuberculosis if it can be shown that its faulty development or impaired vigor is due to an underlying tuberculous infection. Too frequently repeated "colds" in persons of all ages, who are meanwhile never just quite well, or who tolerate the winters poorly, often mean active tuberculosis, of a low grade, it is true, yet not seldom prolonged for years,—and not a "pretuberculous" condition or one of "latent tuberculosis," as it is sometimes called. Phlyctenular conjunctivitis and tuberculides in children with otherwise complete health are surely evidences of activity if they are expressions of tuberculous infection; as are merely episodes of fever, transitory though these may be. All such clinical manifestations mean that foci of tubercle are exerting an effect on the body. Whenever this happens, and for as long as it happens, we must conceive of the processes concerned as active.

It would appear that at present a large proportion, perhaps the majority of cases of above and similar types are not regarded as instances of active tuberculosis. As just mentioned, "pretuberculosis" and "latent tuberculosis" are favorite characterizations of them, as physicians await the appearance of more clearly cut manifestations before classing them as active. Every generation of physicians has had its own idea of what set of symptoms must be arrived at before a condition attained the dignity of "phthisis" or, now, active pulmonary tuberculosis. A century ago Bayle dated the disease from the appearance of "cough, general malaise, and febrile episodes": this was his *phthisic commençante*. But he did come across pulmonary tuberculous foci in the cadavers of subjects who had not reached this incipient symptomatology. This state of affairs he designated *phthisie occulte, ou germe de la phthisie*. He told how subjects with occult phthisis had no symptoms *that would make one suspect* that they had phthisis (*aucun symptôme ne fait craindre la phthisie*). Yet when we examine Bayle's protocols we find that his patients had symptoms enough,—repeated "colds," amenorrhoea, cough, fever, etc.—well nourished and vigorous though they ap-

peared; and, indeed, we may be certain that some of Bayle's patients exhibiting his "germ of phthisis" really died of miliary tuberculosis.

The trouble was that Bayle had too sharp and rigid an idea of how a patient must "shape up" clinically in order to be regarded as phthisical. Like all older physicians it was difficult, yes impossible, for him to think of phthisis without its falling off in flesh and vigor. Notwithstanding our long strides in the century since Bayle, we are now and again impressed with the traces of the old point of view that remain today,—to the great detriment of good diagnosis in tuberculosis; only now attention is centered on the body temperature. And, just as we so frequently read of patients under treatment having their classification changed to quiescent, or arrested, or inactive, upon the return of temperature to normal, and ostensibly on this basis alone, so we find numbers of physicians apparently unable to comprehend tuberculosis as active unless and until the temperature is elevated. It will mark a great advance in diagnosis when the generality of medical men give up the idea that elevation of temperature is the chief and most significant symptom of pulmonary tuberculosis, or the *sine qua non* of activity. Although this not a disquisition on *Diagnosis* it may not be out of place here to plead for the exaltation of fatigability, loss of tone, disinclination to face accustomed tasks, to the captaincy of the motley host of the symptoms of tuberculosis. It is a real tragedy to contemplate the myriads of patients that have passed through this portal into active chronic phthisis, and then for months and years proceeded to advanced stages before tuberculosis was recognized.

This whole subject is so important, especially to any appreciation of *Pathogenesis,* that we may repeat that in practice we will err least if we allow no slightest evidence of lapse from function and efficiency to escape our notice, and if, when it appears in association with demonstrable tuberculous infection, we think clearly in terms of *active* tuberculosis, and proceed accordingly,—treat the patient for the disease.

One parting example of activity, as we sketch no clinical rarity.

We have all listened to the story of the patient,—as bit by bit it has come out in the history,—how his life long he has shunned vigorous exercise or not over-arduous work, because he never felt good after performing it. Or how little by little he has sought lighter occupations and less exacting responsibilities for the same reason. It is remarkable how these men and women, whose slowly evolving tuberculosis takes years to send them to the physician, gradually, unconsciously, and almost imperceptibly to themselves, adjust with measurable success their duties to their waning capabilities, and make a passable accommodation between their tasks and their tuberculosis, which is thus kept just barely below the clinical horizon. Actually it is at the threshold, and at times across. But the patient is never sufficiently aware of the unwelcome guest. He makes another concession, one more reduction of effort somewhere, achieves tolerable comfort once more, and goes along anew but at

slackened pace. Now and then all this comes out in the history with almost diagnostic circumstantiality.

Factors of Environment in Pathogenesis

What shall we say about the pathogenesis of such cases? Roughly, they constitute a type that is by no means a curiosity of the clinic. As we follow the patients through the years, we find that, if they are fortunately circumstanced economically and temperamentally, they can, in a way, shape the course of their tuberculosis at will. By living at a certain pace they are almost sure to bring on the evidences of active tuberculosis,—symptoms of illness and incapacity for ordinary tasks; by proceeding at more measured and careful gait, they lull their infection into quiescence and inactivity, and go about their daily round comfortably and without effort. It is plain that these patients cannot harbor tubercle bacilli or tuberculous foci that are *intrinsically* pathogenic, that is, of a type that *ensures* manifest and progressive disease. *Potentially the germs or foci are so; but not by nature and inevitably.* It is likewise obvious that constitutionally the patients are not of a kind that their tissues are over-prone to the infection or proof against it. Or, at any rate, our enlarging clinical experience would teach us with how little confidence we may interpret the so-called *innate* resistance of the patient in terms of size or extent or even structure of foci in chronic tuberculosis.

Focal Changes in Pathogenesis: In chronic tuberculosis foci of tubercle usually show well-marked, if not predominant, evidences of fibrosis. This peripheral investment operates *toward* preventing extension and multiplication of the anatomical process as well as *toward* impeding the escape of focal material out into the surrounding tissues, there to be absorbed into the system. For foci to extend or for focal products to be absorbed is to follow the path that leads to pathogenesis. We accordingly find that the play of environment, as it influences physiological conditions in the immediate neighborhood of tuberculous foci, is a momentous factor in producing effects that may be expressed clinically.

Exalt the circulation (and therefore the flow and content of lymph) in the affected region; and you promote the sending over to the body of intra-focal poisons as well as the outsweep of bacilli which had been more securely interned before. The circumtubercular circulation will be influenced by as many and as different agencies as can operate in the proper way directly upon any affected part or indirectly through the intermediation of the body: as, for instance, by a local catarrh or congestion, by trauma of the part, by whatever accelerates or deepens respiration in the case of pulmonary tubercle, by fever, by bodily overactivity, by the second stage of parturition, by tuberculin. In actual life the "trick is turned" by local injury, by intercurrent disease, by excessive bodily or organic stress. If we wish, we may take the well and noncomplaining patient, and with tuberculin activate his tubercle; and bring on râles and illness where neither existed before, and tell-tale densities on the X-ray film; and do all

this, perhaps, for only a day or two. Transitory though the upset has been this is pathogenesis, though an artificial pathogenesis, as surely as is the catapulting of an always healthy man into florid tuberculous pneumonia. That is to say, it is pathogenesis qualitatively and in essence; and there is every reason to believe that the pathological physiology concerned in bringing on the attacks of illness is similar in the two instances. Nor will the pathological anatomy show *essential* differences in fundamental characteristics.

Or Marcus Paterson would put his asymptomatic patients at work, designedly to get the same effects. Or our patients under treatment transgress the limits of their prescription for exercise, and fall ill similarly. They activate what has been quiescent; or add to an activity of lesser degree, and thus modify, that is, intensify pathogenesis.

Environment: It might seem unpardonable to labor a point that has latterly become so well understood, were it not for the purpose of laying down sharply the fundamental concept that common to the pathogenesis of tuberculosis, and *quite likely necessary to it*, is the factor of environmental agency or force. In the whole etiology of manifest tuberculosis, it is the factor about which we can speak with the greatest certainty. It has the sanction of soundest and best authenticated clinical experience; and in the realm of probabilities of human tuberculosis we should regard nothing as a fact unless it can be substantiated in the case of the human patient, no matter how absolute or unfailing a particular it can be proved to be apart from the patient—as, for instance, in the animal of experiment.

The structure of tubercle becomes important in pathogenesis only as its environment is considered and is brought into relation with it; and this, too, in terms of place, episode, and time.

Tuberculosis of the lymph nodes of the neck not infrequently is seen to become manifest, that is, *pathogenic*, following an acute inflammation of the throat,—tonsillitis, for instance, or scarlet fever. An occasional onset of pulmonary tuberculosis during pregnancy, or after pregnancy or parturition, is certainly more than casual, as is a not uncommon sequel of tuberculosis to measles. We are quite likely correct in regarding these cases of manifest tuberculosis as brought about by the physiological disturbance of existing and previously inactive tuberculous foci and the tissues roundabout, engendered by the intercurrent experience.

It might be asked why, if measles or pregnancy or any other experience can activate tubercle, one or the other will not always do so whenever it is suffered. The answer is that, so far as we know, the influence exerted upon tubercle is in no instance a specific one; again, that it must be regarded as quite variable quantitatively and therefore capable of a wide range of effects; but, above all, that the intercurrent episode can hardly, in the very nature of things, be always exerting its effects on tubercles that are structurally similar.

Quantitatively, the stresses of life are of every degree, and it must be

the truth that a certain structural conformation and constitution of tubercle are capable of withstanding a certain quantum of stress, without giving rise to manifestations of tuberculosis, at times when they would respond more eloquently to greater stress. But, very important, too, is the circumstance that, unless the formation is completely healed, we may never regard tubercle as having a perfectly fixed and stable structure. As we have said, foci of tubercle go through well-recognized cycles of development and subsidence. Considered as an infection, tubercle may be always tubercle, one and the same; but in construction it is interminably varied, and quite likely never exactly the same at two different times. So, now comes into the foreground the preponderant importance of the element of time in contributing to the issue of a tuberculous infection. A child may suffer measles or a woman enter upon pregnancy at a time when the structure of tubercle which they harbor is influenced with comparative ease, to result in manifest tuberculosis. A few months or a year later the identical tuberculous process might be so constituted, so well sclerosed, let us say, that identical experiences, undergone then, would pass without noticeable effect. As I have said (in substance) in another place: In contributing to breakdown from tuberculosis, it matters a great deal whether a child contracts measles, or an athlete runs a hard race, or a woman becomes pregnant at a "good" time or a "bad" time, so far as the anatomical condition of concealed tubercle is concerned.

Localization of Foci: In the pathogenesis of tuberculosis the part played by the location of tuberculous foci is frequently decisive, and can be almost dramatic. Generalized miliary tuberculosis strikes down most commonly (if we except infants) persons who have previously had no manifest tuberculosis. It is the disease in its most fatal form; and in any number of instances (the proportion depending upon the thoroughness of search) we are permitted, fortunately, to trace the series of events leading to the catastrophe with exceptional clarity and definiteness. In the circumstances it is difficult to understand how any observer can read a so-called lack of resistance into the pathogenesis of this gravest of manifestations of tuberculous infection.

For generalized miliary tuberculosis invariably springs from some antecedent focus within the body; and, when we can detect this focus, we find, again almost invariably, that it was in intimate association with a natural channel of conveyance to all parts of the body. In many instances the retroperitoneal lymph nodes have been involved. Set against the great lymphatic trunks, they caseate, break down, and erupt into the thoracic duct. Now, if the material discharged is enough, it is carried to all parts of the body, to originate widespread infection and disease.

Here is a caseating tuberculous process, contained within its fibrosing investment, and passing without effect, and unnoticed so long as it is so restrained. If the fibrous envelope holds, then in the majority of cases it will remain a case of inactive tuberculosis, to be discovered fortuitously

only at autopsy. Yet a break into the thoracic duct means fulminant disease and death. *Location, and location alone, determines the particular issue.*

It will perhaps be instructive to compare with such lymphatic tuberculosis the series of events put in motion by another common tuberculous process that is intrinsically similar. Here, now, is cervical tuberculous lymphadenitis. Being superficial, it is manifest by reason of tumefaction and perhaps tenderness and softening. The patient is in constitutional health, yet we recognize this as manifest or clinical tuberculosis, that is, infection become pathogenic, because it is superficial and obtrusive (and consequently symptomatic). If it were situated in the depths of the body, as in the case of retroperitoneal lymph-node infection, we would not recognize the condition as pathogenic as long as the bearer remained outwardly well.

Ceteris paribus, and if the foci in both places were evolving progressively, there can be no doubt about the complete antithesis of ultimate prognosis, if each went on to a break. Yet we are in ignorance of the existence of the graver focus (that is, graver prognostically), and for the time being view the less momentous condition with concern. Now the cervical lymph nodes break down and discharge, accomplish what amounts to a surgical evacuation of contents to the outside, and the patient, if anything, may be improved thereby. Could there be any better examples of infection made pathogenic by location, or of outcome entirely contingent upon location?

Or, let us turn for a moment to the pathogenesis of another form of tuberculosis. The tracheobronchial lymph nodes are now infected. Tubercle has long smouldered mutely, and gradually gone over to caseation. The time comes when it breaks through, motivated perhaps by a grippal attack, or prolonged excess of bodily effort, or, it may be, for no discoverable reason,—and, although the way is open for evacuation to the outside, for some reason or other most of the material is aspirated, and the result is a precipitate onset of *phthisis florida*. Location, and perhaps a fortuitous aspiration rather than expectoration, have determined pathogenesis, or, at least, determined the course the infection is going to take.

A patient falls ill with tuberculous meningitis, and dies. At autopsy we observe little that is wrong or significant, except a stippling of minute tubercles at the base of the brain, and, if we are lucky, an old solitary fibrocaseocalcareous tubercle, the parent focus, in a lung or the tracheobronchial lymph nodes. The meningeal tubercles may be so minute that we must use a cross-light to distinguish them. Surely, we think, these foci, of themselves, can hardly be of a kind, or large or numerous enough, to set up disease, much less kill. We are confident that, placed at any other place in the body, they would cause no noticeable trouble; yet put in the basal meninges they lead to the pathogenesis of tuberculosis at its worst.

We see the tuberculous nodule in the larynx break down the patient with serious disease, while we reflect that with the same nodule in a lymph node, or even in his lung, the same patient would be, and likely remain, a well

man. Or, in the lung itself, we observe, peripherally and out near the pleura, a fibrocaseous nodule, or sizable collection of nodules, that have leisurely held their own and made their way, with never a sign or symptom to disturb the fit and vigorous host, whose neighbor perhaps has had the ill fortune to have tubercle, similar to all appearances, settle down more centrally, and developing from and incorporated in the adventitia of a blood-vessel of importance. Under stress the vessel gives way; there is a pathogenesis of tuberculosis with hemoptysis, maybe out of a clear sky; there ensues an extensive aspiration of blood and of focal detritus; and acute tuberculous pneumonia is at hand.

In the shaping of any tuberculous infection, let any and every conceivable significant attribute of parasite and of host have due weight,—there still remains a part, and perhaps a preponderant part for location of focus,—of first focus and of subsequent foci,—to play. In thinking of tuberculosis as a developing infection, we must remember that, from the moment of first infection, what characterizes, indeed creates, its so-called progressiveness is its spreading and its ability to spread; and too that between initial focalization and first pathogenesis there has, in nearly every instance, been some extension or spread. If tuberculous infection is to spread it must have its pathways, along which it may be conveyed. In actual life, these will be of greater or less accessibility in relation to first foci; destinations to which they lead will be of graver or lighter moment with respect to possibilities that may ensue; the distances of first foci from portentous structures will be further or nearer; the lines of defense, of arrest and interception of parasites, such as offered by lymph nodes, between first foci and organs whose involvement spells trouble, will be more or less numerous, more or less impedient, more or less tightly drawn; the tissue in which first foci dwell will be more or less vascular by nature, or its native consistence offer more or less resistance to the encroachment of tubercle (bone, epididymis, lung); the organ involved will be relatively isolated and self-contained, or possessed of far-flung channels of communication, as is the lung. Given, then, first foci or descendant foci, conditioned by location; given, again, a changing focal structure; given, in addition, the almost infinite possibilities of the play of environment or experience upon foci of varied structure, foci in being in a diversity of locations, and always in suitable or unsuitable temporal relations; given all this, and one begins to set the stage for the course that tuberculous infection is to take. It is all this that has something to do in the pathogenesis, as against the continued dormancy, of every case of tuberculosis.

Factors of Constitution of Host

Tendency to Fibrosis: Yet there must be a great deal more at work. You will undoubtedly bear down hard that, thus far, in attempting to resolve pathogenesis, I have been dealing largely with results, and products, and effects, and have evaded the real fundamental forces that must be at work in the taking hold of tubercle bacilli, the establishment of foci of tubercle,

the subsequent evolution or termination of these latter, and the deleterious rather than harmless effects upon the body. It may be granted that sclerosis of foci makes for inactivity of infection, but what makes for fibrosis uppermost rather than the destructive features of tubercle? Once there is established a fibrosis that is sufficient to keep foci silent, it is understandable how, under the influence of focal and bodily environment, it can be upset toward pathogenesis or fortified toward still more secure inactivity of foci.

Conceivably, a tendency toward focal fibrosis rather than its opposite condition is contingent upon attributes of either or both of the two parties concerned in every tuberculous infection, that is, of parasite and host. If such is the case, it has never been demonstrated as a direct and decisive scientific fact. Nevertheless, the enquirer may be allowed to indulge in attractive speculation, as he attempts to marshal and correlate from the clinic and the bench of experiment scraps of information that may apply to the case in hand. But, before entering upon this diversion, it will surely be pertinent, and perhaps helpful, to set down a point of view that is fundamental to any appreciation of the pathogenesis of tuberculosis in all its phases.

Tuberculosis a Self-Healing Process: It begins with the idea that tuberculosis is eminently a *self-healing process*. This is an opinion that has frequently been expressed, and one that is as evidential as can be. Almost as soon as they are established, all foci of tubercle begin to undergo peripheral fibrosis. Indeed, fibrosis is a part of the normal development of every formation, no matter what the type, by which the tissues react to tubercle bacilli. Normally, and *within the same foci*, we find fibrosis of every degree and extent accompanying destructive processes of every variety. Side by side, within the same organ, we may observe foci going on to complete scarring while neighboring foci are in a state of fulminating progression. Within the same body foci in one organ will be healing as those in another part are exhibiting the signs of floridity.

Experience suggests that the normal tendency of the human body is to heal, or at least hold in check, tuberculous infection received in the ordinary or average way; that is, infections of the usual kind and dosage, resulting from the usual contacts that give rise to infection in our civilization. Experience suggests this because it shows that only the veriest fraction of all infections eventuate in clinical disease.

Cattle contract tuberculosis,—as an infection, apparently as readily as mankind; and cattle break down with tuberculosis. But again in cattle the tendency to repair is so outspoken that the characteristic anatomical response is a focal deposition of lime-salts marked enough to give the typical disease the name of *Pearl Disease*. Foci of this nature are an outstanding feature of even progressive tuberculosis in cattle. We derive our ideas of the high suspectibility of cattle to tuberculosis not from range cattle in a state of nature, but from cattle under artificial conditions,—stabled and forced

to lactate. We may well ask whether infected cattle allowed to range would, in general, go the way of progressive disease, and we may well believe that they would not. It is at least a fair guess that, relieved of the stresses of the present conditions of domestication, cattle would take care of their tuberculosis well and suffer breakdown in comparatively few instances.

The Alleged Hypersusceptibility of Primitive Peoples: We dally with the same idea in reflecting upon human tuberculosis. Out of a single fact numerous writers have built up a rather stiff doctrine that avers an exceptional lack of *innate* resistance of primitive peoples to tuberculosis. The basic fact is the common observation that the introduction of tuberculosis among less civilized populations is followed by excessive mortality, the result of comparatively acute illness. The fact is conceded; the conclusion stated is not denied; yet it is submitted that it *need* not follow from the premise; and it is maintained that the premise does not prove it.

And it is suggested that circumstances other than *innate* lack of resistance, circumstances too that are facts, may contribute toward rendering tuberculosis unusually destructive and fatal for those of low civilizations, —at any rate for those who come in contact with the whites of Europe and America.

Judged by our standards, the common living habits of savages and semi-savages are inordinately dirty. At any rate they are supremely adapted to the contracting and spread of bacterial diseases, particularly one like tuberculosis, unique among infections in that it can be contracted in every conceivable way, *via* every possible portal of entry, directly and through an intermediary carrier. The common bowl without individual utensils at meals; the intimate herding at sleep; the windowless, chimneyless, never-cleaned, littered habitations, if dwellings there are; the unwashed, oiled and pomaded bodies or the filthy rags if clothes are worn, must individually and together be regarded as hot-houses of infection, if tubercle bacilli are loose. We cannot imagine a more fertile soil in which to spread an infection; as for tuberculosis, all that is needed is the sowing of the bacillus. And, if seed-time ever does come it will be marked by extreme dissemination and quantity of germs.

Through ages of experience, through trial and error, every savage race arrives at a mode of life that represents the nicest adaptation to the environment in which it dwells. Indeed, a perfection of adaptation has been absolutely necessary to racial survival; and in the course of generations a complexity of habits and customs becomes delicately attuned, one with another, into an harmonious whole mode of life. Left to himself and in the environment which his forbears have learned to control, the savage will flourish. But any intimate contact with a higher civilization will soon put the savage in jeopardy. It will do this not so much by reason of a greater might and ruthlessness of the white man, as by disturbing at critical points the savage's way of living. If brought into the white man's civilization the savage will find it impossible to make a successful abrupt adjustment to his new surroundings. If, on the other

hand, the white man carries his own civilization to the savage, or forces it upon him, there enter the savage's life new elements that are out of step with those practices that arose through the necessities of coping with Nature. In the abstract, houses mean shelter, and clothing protection from the elements, and are therefore features of existence that should spare the body and conserve it; but to the naked savage, dwelling for generations in the open, any gratuitous and rapid transition to houses and clothing can actually spell added filth and weakening of physical tone. Moreover, to use houses and clothing successfully presupposes that the inexpert savage make other changes and adjustments in his habits that would hardly occur to the white man.

Any primitive people, in process of more or less unnatural change of civilization, will run into extraordinary danger if, during the period, tuberculosis is introduced among them. And, as a matter of fact, first racial contacts with tuberculosis are likely to be made when radical changes in mode of living are impending or in progress, for both arise out of first intimate associations of "backward" races with white men. History will not show a single example of a primitive people continuing along the line of improvement in physique and natural development after it had come under the influence of people of a higher civilization. The inevitable result has been physical degeneration and decay of the pure stock, whether American Indian, Polynesian, Bantu or Hottentot.

Whenever, therefore, we take up for consideration the acuteness of disease and the excessive tuberculosis mortality observed among "backward" peoples, attempts at explanation should pay attention to those actual circumstances which we know enhance the chances of gravity of tuberculous infection. We should certainly seek to give these their due weight, if they can be established as facts. At any rate we may not jump summarily to hard and fast opinions of innate susceptibility, any more than we may dismiss offhand the possibility so long as the ascertained facts are as meagre as they are today.

But, continuing the same line of speculation, we may imagine that, in some way or other, tuberculosis entered the midst of a primitive civilization, whose perfectly adapted life—that mode which assured racial integrity and survival—did not change, and remained outside the debilitating influences of more advanced civilizations. For the reason given above, such an event has probably never happened. But, if it could take place, we may suppose that the entire story of tuberculosis in the savage would be totally different from the one that we are accustomed to tell. We might be bold enough to predict that his success in his struggle for existence would have its effect on his tuberculous infection, and that this too he might keep under measurable control.

And, continuing now our speculation to the case of more-advanced mankind, we incline more and more to the view that the pathogenesis of tuberculosis in civilized modern man but expresses the yielding of the individual man to the demands, the stresses, of civilization. We have long realized that tu-

berculosis is a price entailed by civilization in refining man,—in taking him from more natural pursuits and putting him under the more artificial complexities of modern existence. We are impressed with the inherent marked tendency of the tuberculous process toward healing. We observe, even in our strenuous civilization, the vast majority of infections buried below the level of pathogenesis. May we not therefore suppose that, except for rather fortuitous and mainly extraneous circumstances, as these affect the individual, tuberculosis would always remain nonpathogenic? Is not such a point of view more probable than one which would conceive of tuberculosis as essentially possessed of a dynamic quality that sends it on to progressiveness,—along a course that is to be prevented only by active intervention somewhere along the line? Should not our admonition be "Don't do certain things if you would avoid tuberculosis," rather than "Do this or that to prevent tuberculosis?"

Innate Differences of Constitution: Coming now to individuals, we may not doubt that because of innate differences of constitution human beings differ in their anatomical responses to tubercle bacilli which infect them. Difficult, yes impossible, though it is to prove in a scientific sense, the opinion is a necessary derivation of the simplest and plainest evidence. It will hardly be questioned that the characteristic anatomical effect of tubercle bacilli, that is, nodular tubercle, represents the tissues' native mode of reacting to a stimulus or irritation exerted by the parasites. There can be even less doubt that mankind reacts to many, perhaps all, types of irritation in an individual manner, a manner that is anatomically varied, and varied because of differences of inherited reactivity of tissues. We observe this phenomenon exhibited strikingly and decisively upon bodily exposure to the rays of the sun. The surgeon notices the healing of similar wounds take place differently in different people, yet more or less typically and according to rule for the individual person; a personal, connoting an inherited, tendency to keloid is a striking example. It is stretching probability not at all to suppose that the native capacity of tissues to react fibrously to injury of any and every kind varies with the individual constitution. We know that in general it changes normally with growth and maturity and senescence, becoming greater with advancing age, —a circumstance that conceivably plays no small part in the alleged increase of resistance to tuberculosis that attends the natural aging of man. What is, of course, important in this connection is that individual variations of tissue capacity for fibrosis would surely affect pathogenesis in the individual case.

Gout and Tuberculosis: Gout is among the most plainly inherited diseases in the sense that it makes its appearance in soil that is prepared by constitution transmitted by ancestry. The characteristic gouty type is known to all. Stocky build, short, thick neck, florid complexion, sandy hair,—these features will often enable one to pick out the gouty from among total strangers. Why they should be associated with a relative inability to metabolize

purins is entirely unknown; but the fact remains, as does the well-established clinical observation that the gouty either do not fall ill with tuberculosis, or that, showing activity, they resist the disease exceptionally well. Is this over-resistance to tuberculous infection owing to the heaping up of urates, itself the effect of inefficient purin metabolism?—old experiments failed to establish this relationship. Or is it conditioned by the same defect as is the metabolic fault?—or by some other one or several of the physical attributes that mark the gouty as a type? Whatever might be the answer to such fascinating problems so clearly presented to us in actual life, one can hardly avoid the conclusion that in the case of the gouty we are dealing with individuals in whom the pathogenesis (here the nonpathogenesis) of tuberculosis is affected by inherited constitutional determinants.

Diabetes and Tuberculosis: We find ourselves thinking similarly in regard to diabetes mellitus, though in his resistance to tuberculosis the diabetic's position is opposite to that of the man of gouty tendency: he is oversusceptible to the infection, just as he is to other focal, for instance, staphylococcic infections. Experiments, designed to show that the flaring of tuberculosis in the diabetic organism is the result of exuberant growth of tubercle bacilli in a favoring culture medium created by sugar-rich tissues, have not got far: at least, they have failed to bring any support to such an explanation. In our ignorance, it is at any rate significant that diabetes, also a so-called disease of metabolism, is associated with an unusual tendency to active tuberculosis,—this coupled with the frequently great probability that diabetes is conditioned by inherited physical factors.

Obesity and Tuberculosis: The physical tokens of predisposition to diabetes are not so well marked as in the gouty, yet out of relationships, which are as yet ill-defined and obscure, though by no means concealed, there does emerge one which often elicits comment. This is the occurrence of diabetes in the obese and in the members of families inclined to obesity, one of our most clearly inherited bodily aberrations. What now becomes of interest is the undeniable fact that obesity provides peculiarly sterile soil for tuberculous infection. How it does this is thoroughly inexplicable. It is all very well to say that active tuberculosis is caused or promoted by insufficient nutrition, an etiological relationship that has never been proved, though the antecedent or coincident association is frequent enough; or to maintain that overnutrition prevents or arrests the disease, again a common concurrence yet unproved causal sequence of events: the statement explains nothing, and does no more than recognize the important fact that poor nutrition and active tuberculosis go hand in hand, and *vice versa*.

Nevertheless, it may be worthy of note that we see active tuberculosis develop much less frequently in the obese than become arrested in them. In other words, in fat or overfat persons there does seem to be some impediment to the pathogenesis of tuberculosis, while it is not so noticeable that an achieved obesity will arrest an established active tuberculosis; for nu-

merous are the cases in which the disease, even when of only moderate degree, will remain active in the presence of great overweight; and, frequent, as concerns arrested cases, is the criticism that arrest of disease has not been brought about by the excess of nutrition, but that the latter has resulted from the cessation of intoxication that followed focal improvement caused by rest, and from the physical inactivity and heavy diet employed in treatment.

At any rate, common observation leaves no ground to doubt the exceptionally high resistance of the constitutionally obese to the pathogenesis of tuberculosis, and we comment upon it here as added evidence of the constitutional factor at work in pathogenesis.

Congenital Peculiarities and Anomalies: Congenital anatomical features, peculiarities and anomalies on occasion surely contribute to the pathogenesis of pulmonary tuberculosis. Pulmonary stenosis is a striking example of an inherited fault that promotes the occurrence of active phthisis. Certain types of thoracic conformation or peculiarities of the several divisions of the upper respiratory tract, of a kind that impede or limit respiration, and handed down from generation to generation, conceivably tip the scales toward active tuberculosis, given the proper conditions of infection. The slender, gracile build of body, with disproportionately long extremities and short torso, has always been regarded as oversusceptible to tuberculosis, and perhaps correctly so. For clinical experience becomes impressed with the idea that such subjects, when stricken with tuberculosis, are poorer "risks" than the average. Respiration, made deficient by obstructive hypertrophied tonsils and adenoid growths, must often help to prepare the ground for phthisis, by reason of both its direct pulmonary effects and its general physical depletion; and lymphatic overgrowth frequently "runs in families."

Indeed, scattered hints of the constitutional factor at work in the pathogenesis of tuberculosis are numerous and convincing enough, yet there is an almost entire absence of controlled scientific evidence in proof of the circumstance. Few phases of the subject should today promise a more fascinating inquiry than the constitutional factor and the genetics of tuberculosis. And I am here tempted to repeat what I wrote ten years ago at the close of an essay on *Environment*:

> There is not a little clinical evidence that such diseases (to mention only a few) as gout, epilepsy, migraine and cardio-renal-vascular insufficiency arise on an inherited background. It has always been a byword that longevity is inherited. Nervous instability and overirritability certainly are. And who knows but that nervous irritability, which at bottom must regulate cellular activity in general, will not ultimately be found markedly to influence the origin and development of infections?

Family Tuberculosis: There is no evidence to support the ancient idea that the repeated tuberculization of successive generations of a family reduces in time the resistance of the family's descendants to tuberculosis. On this point we have no facts, one way or the other. But, as regards *specific* immunity to the infection, we

would presume, from what we know of immunity in general, that this should, if anything, be increased by tuberculosis becoming active generation after generation. Indeed, not a few writers are inclined to regard the alleged greater resistance of advanced civilizations to tuberculosis as having been gradually brought about through continued and prolonged contact (infection) with the tubercle bacillus,—an idea to which, in the writer's opinion, our very imperfect knowledge of the epidemiology of tuberculosis brings no support.

Yet, bound up with this question are several basic biological matters, which must ultimately receive consideration and, we hope, elucidation. For instance: Does chronic phthisis, which manifestly influences hormonic activity and which is prominent in its devitalizing constitutional effects, bring about the germinal or placental transmission of debilitating qualities, that nonspecifically lay the body more open to the activities of the tubercle bacillus? May not economic impoverishment, another common accompaniment of chronic phthisis, if recurring generation after generation, lead to waning and depleted vigor of a family, and therefore *presumably* diminished resistance to tuberculosis? Is there an assortative or selective mating going on between individuals of phthisical habitus? If so, would a resulting expected cumulation of nonspecific susceptibility be counterbalanced by a predicted increase of inherited specific immunity?

Few diseases can offer such complexities as will tuberculosis in even its simplest phases. The mildest infection immediately alters the entire body profoundly (it renders the latter allergic and immune). Active disease ebbs and flows throughout the span of a normal lifetime; as, from childhood to old age, in many a passably capable man and woman, the characteristic lineaments of tuberculosis, never perhaps completely dormant, are noticeable in the spare and lax constitution of the victim. So much is fact. May we not therefore be permitted to expect some day the demonstration that bodily function, depressed without let-up, and this in infected parent, in infected child, and again in infected later descendants, will at last put its mark on tissue stock, now inherently altered in its capacity of response to tubercle bacilli? Indeed, how can the case be otherwise?

The Influence of Immunity and Allergy

We may believe that in any case, when the tissues of the human organism first strike contact with living tubercle bacilli, there takes place an interaction of at least three categories of forces, through which will be affected and defined the course of the infection that is about to result. Operable, for instance, will be those native tissue peculiarities bestowed by inheritance. Influential too will be features of the parasite,—virulence, viability, quantity, etc. Perhaps most important in the individual instance will be elements of circumstance and environment:—the localization of the bacilli, the physiological activity of the body and of the circumfocal territory at the time of infection, and so on. Two of these forces may be regarded as fixed quan-

tities, and as exerting a uniform and predictable influence if their measure were determinable: that is to say, inherited constitution and initial aggregate of germs concerned constitute unchanging factors, whose effects should proceed along certain well-defined lines laid down at the time of infection. Contrariwise, for an originating as well as an evolving infection environment is an illimitably variable factor, and, by virtue of its irregularity, it must, we believe, be capable of modifying and altering those characteristics of an infection that are determined by the interplay of native constitution and original parasites. Indeed, for the reason given, environment can hardly act otherwise than as the moulding, yes the directing agency in every tuberculous infection that drags out a dormant and chronic existence within the body,—and this means all but a very few tuberculous infections.

But, as soon as any and every initial infection is established, we are obliged to reckon with two new bodily (tissue) attributes that conceivably affect pathogenesis. As soon as first tubercle is formed, all the tissues acquire a new capacity to react to tubercle bacilli in an acute inflammatory manner. This property, denominated as *allergy*, embodies a condition of tissue *hypersensitiveness* to the protein constituents of the tubercle bacillus. By virtue of the presence of tubercle the body also becomes specifically overresistant, that is, *immune* to fresh implantations of tubercle bacilli or to any further extension of those bacilli that may be already focalized.

As to the identity or nonidentity of tuberculoallergy and tuberculoimmunity, little need be said here. The question is not settled, and the two shall be treated here as separate phenomena. For our purposes immunity is regarded as that condition of increased specific resistance to implantation and extension of tubercle bacilli, and allergy as that state of tissue hypersensitiveness to tuberculoprotein, that come into existence with the earliest formation of specific anatomical tubercle. Both immunity and allergy continue at work within the body as long as tubercle, with its tubercle bacilli, persist.

Immunity: When subjected to careful, controlled observation specific immunity exhibits itself as follows: Infected animals of experiment, when exposed to reinfection, suffer, as a result of the latter, a tuberculosis that for a long time is relatively localized, that (after the subsidence of early acute phases) takes on the anatomicopathological features of chronicity (fibrosis, etc.), that then spreads with great slowness if at all, and that leads to death only after a much delayed evolution of the infection (reinfection). The course of events is in striking contrast to what goes on in normal nonimmune animals given identical inoculations of living tubercle bacilli as first infections: when the first evidences of tubercle come to light tardily, disseminating pathological changes appear with but slight interruption or delay, and generalized tuberculosis carries off the animals within several weeks, or a few months at the latest.

Comments in modern medical literature are marked by a good deal of misconception concerning the manifestations of tuberculoimmunity. One may read statements to the effect that the

tuberculous animal, being immune, cannot be reinfected (unless perhaps by excessive quantities of tubercle bacilli,—so-called "massive dosage,"—when immunity is said to break down); and many contributions on the etiology, immunology and pathology of tuberculosis imply as much when they use the disclosures of animal experimentation to throw light into the obscure corners of human tuberculosis.

That the immune tuberculous animal cannot be reinfected:—nothing can be farther from the truth. As a matter of fact, the experimenter is impressed by the following striking circumstance: That while the animal with competent immunity plainly puts up an extraordinarily heightened resistance to quite large "doses" of virulent tubercle bacilli, the same animal will present some morbid changes,—tubercle, in other words,—in response to reinfection with small, yes minimal, "doses." What is to be observed in the latter instance is not a complete warding off of impending infection, a total refractoriness to a "taking hold" by the germs. Some tubercle is almost bound to result,—a fact that is all-important to our understanding of tuberculoimmunity, and especially to our efforts to give this immunity its proper and significant place in the scheme of human infection and disease.

For it must be obvious that such tuberculous processes, arising in immune soil and developing under the restraints and impediments of the forces of immunity, whatever these may be, will frequently be of a kind, a quality, and of an extent, let us say, or, accidentally placed, may spring up at a portentous site, that bid fair to lead to trouble; that is, deranged function,—symptoms,—pathogenesis. Certain it is too that such anatomical formations, born of the response of immune tissues to moderate or ordinary deposits of tubercle bacilli, can on occasion last long enough to cause trouble. Often, when working with immune tuberculous animals in the laboratory, we find that reinfections with few bacilli (in the skin, where events are always under observation) are followed by first, local acute inflammation, which, subsiding, gives way to a nodule (tubercle) of precocious appearance and evolution; and now, the nodule, ulcerating comparatively early, takes on an umbilicated or eccentric bowl-shaped conformation, and remains weeks and months, irregularly rimmed by thickening fibrosis and slowly closing in its denuded pitted centre. Meanwhile, the high immunity of the animal is displayed by the fact that the tubercles of reinfection are confined to the site of inoculation, that is, where the healing ulcer dwells, throughout a period when identically inoculated animals of first infection are dying of thoroughly generalized tuberculosis.

Often, as we watch this series of events, we cannot help wondering how such a process, a slowly healing ulcerated tubercle, an "immunity tubercle" let us call it, would affect the human patient if, instead of in a guinea pig's skin, it had its birth in the former's lung. Now, too, as a human pulmonary focus, it would be "played upon" by all the physiological vicissitudes and shifts and stresses that constitutionally and organically are part of the daily life of every person

alive,—by all the circulatory and respiratory ups and downs that go with every grade of physical and psychical activity, with intercurrent bodily and organic disease. It is not to be doubted that frequently such tubercle would be pathogenic.

Briefly, the result of tuberculoimmunity becomes manifest as a *modification* of the course of a process that would be characteristically progressive in the nonimmune animal, and this modification is expressed in greater chronicity and circumscription of resulting foci, and relative tardiness of the latter's spread. We know, we recognize, tuberculoimmunity only through its effects,—through the observation of tuberculous infection held at a standstill, or pursuing a chronic progression, or taking the path of retrogression in the individual animal (human being). *This immunity becomes part of every tuberculous process as soon as the latter gets well under way.* Indeed, with infrequent exceptions, it directs, in a measure, most human infections received under the conditions erected by our civilization. For the vast majority of the white man's infections are held permanently in check, as too the preponderant number of active cases are marked by discrete focalization and chronicity far more than by unchecked and far-flung generalization. Perhaps it is this immunity which makes of tuberculosis the characteristically healing infection upon which we have dilated above in our discussion of inherited factors. Coming early into operation in every initial infection, in our civilization it acts as a force which is ordinarily sufficient to stay the unbridled effects *of those numbers and types of bacilli that are the average for first infections of our civilization or fall below this average.* Without such an opposing agent the average of quantity and virulence would, we may believe, lead to a rapidly fatal issue.

Allergy: But as to the mechanism of tuberculoimmunity we can speak with little certainty. Of all the varied so-called "immune phenomena" that modern Immunology has disclosed, one, and only one, process seems to bear any uniform relationship with immunity, if we restrict the term *immunity* to a condition of specifically increased resistance to implantation and extension of tubercle bacilli. Allergy alone appears and acts in a way that leads one to associate it with immunity.

As with immunity, the presence of anatomical tubercle is necessary for the existence of allergy. The allergic state is recognizable only through the appearance of the allergic reaction. This reaction is marked characteristically by elements of acute tissue response, by features of acute inflammation. If intense enough, the reaction will result in tissue necrosis (caseation), and there is reason to believe that the necrosis, a destructive phase, of tuberculosis, is brought about by the allergic reaction. But involved in the allergic reaction is also an accelerated proliferation of cells that build up nodular tubercle, and we may regard an enhanced fibrosis of the tuberculous process as one end-result of the reaction.

Accordingly, the allergic reaction is seen to be responsible for all the acute manifestations of tuberculosis, and

when so considered it must be viewed as a potent contributor to pathogenesis. Human beings pass as perfectly well as long as they hold their tuberculous infections asymptomatic, inactive. But they are allergic; and any discharge of sufficient focal material to a new place will render them immediately ill because of the allergic reaction that ensues promptly.

Allergy Creates Symptomatology: Indeed, after we artificially infect an animal for the first time, we do not find it exhibiting symptoms of illness until the allergic state is established by the infection. Or, just as significant, the only animals that can be rendered ill by inoculations of tubercle bacilli or tuberculoprotein (tuberculin), are tuberculous, that is, allergic animals. Enormous doses of tuberculin or quantities of living tubercle bacilli are borne by nontuberculous animals without the slightest appreciable effect (except that tubercle will eventually result from inoculated bacilli). Minute doses of either will precipitate severe illness in animals with tubercle, and moderate doses will kill the animals.

Here then is the clue to much of the symptomatology of the disease tuberculosis. Not a little of it is the expression of allergy in reaction. The infected patient, long harboring tubercle and perfectly well just as long, has perhaps a few bacilli set in motion and sent to a new location, or at a long-quiescent, asymptomatic focus he has an excess of bacillary protein react with focal tissue to set up an acute focal reaction. The result is an accession of malaise and fever, with perhaps cough and expectoration. These symptoms may last only for the day or for a week or less, and die down never to be repeated, or they may recur again and again until a more permanent state of illness is reached. All this is pathogenesis of various types; but the more transitory episodes are only too likely to go unrecognized and escape a true appraisal until recalled after the more settled and prolonged illness is diagnosed correctly.

Evidence That Allergy Leads to Immune Effects: The course of every tuberculous infection is punctuated by allergic reactions, which are capable of every conceivable degree of vigor, intensity and duration. The experimenter, working under designed conditions of control and in a position to follow through his experiments to their ultimate issue, finds that all allergic animals, made ill by fresh reinfections, come through with much less anatomical tuberculosis, if they survive their acute illness, than do the originally normal controls given the same infections (as first infections) and not made acutely ill by them. For this reason he can hardly help viewing allergy as a resisting, a conservative, process, true though it is that in the operation of allergy the animal is made ill, and on occasion to a degree that may put life in jeopardy. Greater experience indeed leads him further to think of the symptoms of illness, especially the more acute symptoms, as expressions of tuberculoimmunity at work, and he recalls Wolff-Eisner's paradox of many years ago,—that the beginning of symptoms of typhoid fever means the beginning of its immune period. Going still further, the

experimenter asks, "What then is the incubation period of an infection unless it be that interval after infection during which immunity is being established?"

For in the allergic reaction he observes brought into play enhanced, exaggerated and greatly accelerated responses of the tissues. He gains the impression that these promote the fixation of germs let loose, and thus act in a way that hems them in and bars the further spread of bacilli, which, were it not for the impediment set up by the allergic reaction, would go rapidly to many points and thus give rise to more generalized tuberculosis. As a matter of fact, this much he can demonstrate by planned experiment. And, appreciating that concepts of immunity are derived from observations of comparative immobility of foci and restriction of infection, he finds in allergy a force that leads to the semblance, the effigy of immunity, in that the allergic reaction impedes the extension of infection. To all who would voice their inability to comprehend how processes of destruction (necrosis) and disabled function, and even death itself, can be brought into any accord with concepts of immunity, he would reply that he stands on two unquestioned fundamental facts. These are, first, that only the tuberculous, therefore the immune *and* the allergic, animal can respond with acute inflammation and necrosis to tuberculoprotein and to tubercle bacilli; and, second, that the *normal*, nontuberculous animal cannot be made ill by tuberculoprotein or tubercle bacilli, while the tuberculous, immune, allergic animal is almost immediately upset by either. To this may be added the further important circumstance that the tuberculous, immune, allergic animal, subjected to reinfection and rendered acutely ill thereby, will, if it survives the illness, long outlive the nontuberculous, nonimmune, nonallergic animal that receives, without suffering symptoms, an identical infection by way of its first infection.

In ordinary active tuberculosis there is, we believe, a constitutional symptomatology set up by absorbed focal products, which, as nonspecific degraded proteins of all the cellular components of foci, act as poisons, and intoxicate. But there can be no question that tuberculosis has also its specific symptomatology. This latter is expressed most plainly when foci erupt and discharge their contents to other places. The fresh deposition of focal material is now on sensitized (allergic) soil. If enough focal contents are brought to bear, are concentrated, upon one limited territory, the result is a violent inflammation coming on abruptly. Exactly this happens when an apical focus, perhaps long sluggish or quiescent, or a caseating hilum process throws its erupted material to midlung, and a tuberculous pneumonia promptly ensues.

Now the illness engendered by such a catastrophe may, as we observe, come on with headlong speed, as from health the victim is struck down with florid symptoms. What happens anatomically is an acute allergic reaction or interaction. Pneumonia quickly involves the tissue roundabout where focal material has settled. In addition, the original offending focus is affected by the material, the antigen, let loose

from it. It too undergoes an acute inflammation; that is, it suffers what is in essence a tuberculin reaction. From it now proceeds material to poison the body and thus contribute to the constitutional symptoms.

We must regard much of this symptomatology as allergic for the reason that we can reproduce it (in experimentation) by using tuberculin or dead bacilli or living bacilli introduced intravenously, and thus sent to the lungs of tuberculous animals. Normal, nontuberculous animals, treated similarly, exhibit no effects.

To sum up: In every established tuberculous infection, we may think of every increase of intrafocal tubercle bacilli or every conveyance of bacilli beyond their focal bounds as met by allergic reactions. In the vast majority of countless instances the numbers of bacilli concerned are too small to lead to appreciable or sensible effects. Their fixation, immobilization, and perhaps partial or complete destruction are accomplished. This end-result is conceived of by us as immunity. Large numbers of bacilli originate more severe to florid reactions, when illness, pathogenesis, now features clinically the "effort" to halt the progression of bacilli (infection), that is, to accomplish again what will appear to us as immunity, if only the patient recovers from the illness. All this is laid bare, and without equivocation, in controlled experiment.

Fulminating Tuberculosis the Expression of Intense Allergo-Immune Action: From this point of view the relatively violent and extensive fulminating processes that are comparatively frequent in infants and members of primitive civilizations cannot be regarded as the manifestations of slight defense, of oversusceptibility, of no immunity. They will now be interpreted as the very reverse. They become the expressions of relatively heavy infections reacting, in soil made excessively sensitive by initially heavy (repeated) infections, with tissues that are extraordinarily sensitive because little time has elapsed since primary infection, fibrosis is immature, and allergy has not had time or opportunity to wane.

Why primitive natives should undergo excessive exposure to infection, given the opportunity of contact, is obvious and has been made plain above. Why of all members of our civilization infants, as a class, should also be inordinately exposed, *if the chances of exposure exist*, should also be self-evident, and need no elaboration. Experiment shows that, after primary tuberculous infection is achieved, it takes two weeks (more or less) to allergize and to immunize the tissues, and do this to a high degree. It has never been shown that our babies or African natives differ in these respects from guinea pigs or rabbits or sheep or any other animals studied. We would therefore postulate that they too are promptly made highly allergic (as can be proved by skin tests) and immune.

Again experiment shows that large or repeated inoculations of tubercle bacilli create a greater allergy and immunity than do small or single applications. They also prove that, in the two weeks or so that are required for the establishment of allergy and immunity, large or repeated infections with tubercle bacilli will lead to more

numerous and more extensive initial foci, with presumably (and actually) more bacilli concerned.

When, now, allergy and immunity do become manifest after relatively heavy (repeated) primary infection, they appear on a stage that is set with an array of focal tubercle and bacilli that is pregnant with vastly greater possibilities as regards allergic tissue reactions and the illness these set up. Here now are just the elements needed for extensive and widespread inflammatory and rapidly necrotizing (caseating) processes; so intense and extensive, indeed, that the patient may quickly succumb before there has been time for measurable fibrosis, or a clearing (resolution) of the pneumonic changes and a later appearance of postpneumonic discrete focal tubercle. The sequence of events is of a piece with that observed in the tuberculized, and therefore allergized and immunized guinea pig, subjected to heavy artificial reinfection. Then there ensues grave, alarming, and often rapidly fatal illness at once. Those animals that die within one day to a week after reinfection exhibit lungs with great coalescing patches of pneumonia, even of a hemorrhagic type if reaction has been extreme and, after three or four days, going over to necrosis. But those that survive the immediate florid illness will without exception outlive any normal nonimmune, nontuberculous controls, which were subjected to identical applications of bacilli by way of first infection and have accepted these without the slightest display of inconvenience or discomfort during the early postinoculation weeks,—that is, until anatomical tubercle resulted.

No, to conceive of *tuberculous* babies or *tuberculous* savages as oversusceptible to tuberculosis is to scrap every bit of scientific evidence of tuberculoimmunity that we possess. They can be no more ultrapredisposed than is the *tuberculous* guinea pig, which we can prove indubitably to be highly immune,—always; and to a degree that varies directly with the vigor and extent of its tuberculous process (until the cachexia of terminal stages depresses all reactivity). And we would lay down the proposition that *the fulminating tuberculosis, that occurs frequently enough to be regarded as somewhat typical of babies and savages, is the expression of an initial heavy-infection tuberculosis extending into or discharged upon oversensitive and overimmune soil.* When the previously healthy civilized adolescent or adult has the ill luck to have long-concealed and never-suspected caseous hilum lymph nodes erupt to all parts of a lung or both lungs, a not dissimilar sequence is precipitated, to wit, that rare disease phthisis florida, always secondary to antecedent focal tubercle, almost invariably encountered in persons without clinical history of earlier tuberculosis, and incontestably arising in an immune body.

Immunity and Allergy Competent under Average Conditions: Most civilized human beings do not go on to active progressive tuberculosis because, as has been hinted, the allergy and immunity aroused by their initial infections are competent to hold in abeyance and quiescence that focal tubercle which is the average resultant of the average kind and numbers of

bacilli concerned in primary infection acquired in the average way and then subjected to the average stresses of environment. As the stresses of environment multiply to sum totals that exceed the average the gates of pathogenesis open to increasing width and permanence; just as, when these stresses are done away with, tuberculosis in the active, the pathogenic, case under treatment, is lulled into quiescence, provided advance has not been so far or decided as to make retreat impossible. On August 1, 1914, the tuberculoimmunity and tuberculoallergy of the German people were no doubt of the same quality and quantity as they had been in 1910 and 1900 and 1880, or for a century. But under the load of wartime conditions morbidity, pathogenesis, leaps ahead at once, and at a rate that doubles and trebles mortality within two or three years. Moreover, pathological reports told of an undue tendency to fulminating types among adult patients. Again, it must be remembered here that, the less there enter into the lives of the individual and the general body of a populace the chances for physical and psychical recuperation and relief, the greater will become the probabilities of occurrence of acute tuberculosis. For then a stern necessity keeps patients at their accustomed tasks the longer before pathogenesis is recognized and treatment is instituted. Then too the same compulsion shortens the periods and hampers the effectiveness of treatment for active disease. As a result, focal fibrosis will diminish in competence, focal extension and eruption be far more frequent and serious, and acute, necrotizing tuberculosis more common. In the case of the city negro indigence and an irresponsibility, that is racial, work hand in hand to the same effect. A tuberculosis that is allowed but inadequate chances to fibrose travels inevitably toward bursting of bounds and toward acuteness. The urban negro, doomed to a life of physical toil and with no more capital than his daily wage, is, in addition, so constituted that he will not drop his tools and seek advice until the symptoms of any disease transcend his endurance; nor will he continue treatment for any disease beyond the time when symptoms are again made bearable,—whether for tuberculosis, syphilis, or even acute pneumonia. In the circumstances the wonder is that he exhibits as often as he does the chronic ulcerating pulmonary tuberculosis that has come to stand as the type for the white adult.

Factors of the Bacillus

Are there attributes of the tubercle bacillus that presumably have their effect in determining which course a given tuberculous infection is going to take,—whether more or less inevitably toward pathogenesis or toward permanent inactivity?

To regard bacillary variables as potent, perhaps the most potent of all elements that conceivably make for pathogenesis in tuberculosis, is, quite likely, the most natural point of view to take. In the early days of bacteriology we were prone to veer to such an opinion still more automatically. As a vista of almost illimitable possibilities of the new era opened, our attention became centered on the para-

site to an extent that for a time neglected the likelihood that qualities of the other party to an infection, the host, might have anything to do with shaping its issue. Accordingly, the first decade or two after the discovery of the tubercle bacillus, devoted so largely to the more precise study of the etiology of the disease, witnessed many an inquiry planned and carried on to interpret the long-recognized and baffling diversity of tuberculosis in terms of the bacillus alone.

Virulence: It can hardly be said that these attempts succeeded. The quality of bacillary virulence first passed under review and experimentation, as investigators sought to correlate the multiplicity of clinical manifestations with a presumed range of parasitisms. They tested the virulence of numerous strains of bacilli isolated from patients with every type of tuberculosis, involving processes that ran the scale from the most inactive, mildest and most chronic, to most severe, fulminant and acute. Their net result served only to arouse the rather unexpected impression that the tubercle bacillus is a germ of remarkably uniform virulence, and one that remains extraordinarily even through the many vicissitudes that years of a chronic infection can conceivably engender.

Then came the detection of the bovine variety of bacillus, and twenty and more arduous years in establishing its place in human infection. It does infect human beings; that was made certain. It does cause manifest human disease; that too has at length been settled. It does on occasion kill; that can no longer be questioned. But in infecting, in making ill, in causing death, does it act any differently from the human bacillus?—and how, and why?

The Bovine Bacillus: The most noteworthy features of bovine-bacillus, as compared with human-bacillus, infection in man have turned out to be a much higher incidence of both infection and disease in childhood than in later life and an extraordinary rarity of progressive pulmonary disease set up by it at any age.

The more common occurrence of bovine infection in early life may be supposed to reflect merely the much greater opportunities of infection through cow's milk in childhood and infancy, when the chances of contact with contaminated milk must be immeasurably greater in both number and magnitude than at any other period of life. We consider this a much more probable explanation of the phenomenon than any view that ascribes it to a hypothetical adult immunity set up by a hypothetical childhood infection. That infants and children ingest much more cow's milk than do adults, and that milk makes up a much larger proportion of their diet are facts. That they take in many more bovine bacilli, and much more frequently and over much longer periods of time, is a strong probability that must follow from the fact. That human adults successfully resist tuberculosis by virtue of a specific immunity based on previously acquired infection has never been demonstrated as a fact. However, the certainty follows from the uniform results of animal experimentation; but from the latter we must also conclude

that the *infected* (by bovine bacilli) child is likewise made more resistant (specifically immune) to succeeding contacts with tubercle (including bovine) bacilli. Indeed, the child, made immune by infection, should be more resistant than the adult, immunized by childhood infection of a similar character, for we have learned (for instance, from cattle immunization) that specific immunity wanes as nonprogressive infection recedes with time. That adults, who can be proved to have a high specific immunity, do acquire clinical infections anew (metastases, for instance) and do not resist active tuberculosis successfully, may be observed again and again in the clinic.

Why do we see so little progressive pulmonary tuberculosis result from human infection with the bovine bacillus? Honesty compels the answer that we don't know why. But we may readily observe another phenomenon that may be pertinent here and significant.

If we inoculate cows intravenously with virulent human bacilli we send the germs to all parts of the body. They settle in the lymph nodes and the joints, and they lodge in the lungs. They may remain alive for years, as they give rise to a slowly evolving focus in a joint that will cripple the animal. Those that become fixed in the lungs may arouse tubercle-formation there. But this is practically always a self-limited process, that reaches a moderate acme and then turns toward healing. In other words, the human bacillus will not cause progresssive pulmonary tuberculosis in cattle.

Why, we don't know. The fact remains. We may in our ignorance say that it is not the *genius* of human tubercle bacilli to set up progressive pulmonary tuberculosis in cattle, which amounts to about the same thing as that human bacilli are natively of comparatively low virulence for the *Bovidae*. And on this slender basis of analogy we may also suppose that it is not the *genius* of bovine bacilli to cause progressive pulmonary tuberculosis in man. Bovine *infection* of the lungs of children undoubtedly occurs, —frequently, and especially in subjects with extensive extrapulmonary bovine foci, but the pulmonary lesions practically never take on the characters of pathogenic processes.

In all animals subjected to experimental inoculation bovine bacilli have been proved to be more virulent than the human type. Since the circumstance holds true even for anthropoid apes, a few writers have postulated that bovine bacilli must be of greater virulence for man likewise. But clinical experience is overwhelmingly against this probability, and must be considered decisive. Yet human infection with these germs of relatively low virulence can illustrate beautifully conditions that will render a bovine-bacillus infection grave and even fatal. Bovine bacilli can lead to death in human beings. But, when they stage this catastrophe it is because they have been carried to places where tuberculous infection is inevitably fatal,— to the meninges, for instance; and we have another instance of the quality, the grade of pathogenesis determined, not by qualities of germ or host, but by location of infection.

The weight of evidence, none of it for obvious reasons based upon direct experiment, is overwhelmingly against a virulence of bovine bacilli for human beings of any age that is greater than that of human bacilli. It is probably much lower; and to this likelihood we would attribute the great decline of bovine infection that takes place between childhood and maturity. Within this interval the ingestion of cow's milk decreases enormously, which simply means that the opportunities for bovine infection must grow proportionately less. Accordingly, the absolute numerical incidence of bovine infections reaches its peak in childhood. Not being replenished, the actual infections in being tend from now on to come to an arrest. Much more:—they retrogress, subside, die out completely and disappear, caused as they are, by a germ of comparatively weak invasiveness; until a bovine-bacillus incidence of, it may be, one-quarter of all infections in childhood becomes transformed into one of one-twentieth or one-fiftieth (or less) of all adult infections.

On the whole we doubt very seriously whether the young stand in a peculiarly hazardous relation to bovine bacilli *per se*. But they are in greater danger of bovine infection because their feeding provides immeasurably greater opportunities for receiving bovine bacilli. From this point of view, and because of our conviction that most bovine infections die out with time, we incline to the belief that bovine infections perform their greatest service in childhood. Then, when most numerous and most vigorous, they protect young human beings against the more virulent human-bacillus infections, and they then do this most perfectly. It is not inconceivable that a prime function might be so to resist human-bacillus contacts as to render the effects of these reinfections minimal, and that then the resulting milder human-bacillus infections that "stick" keep up a more lasting and competent immunity into and through adult life.

One gathers from certain writers that, in children particularly, tuberculosis of certain types, for instance, the lymph nodes or bones, *must* be of bovine-bacillus origin, the argument implying a sort of selective affinity of the bovine bacillus for certain tissues. It should not be difficult to dispose summarily of any assumptions of this nature. The high incidence of lymphatic and osseous tuberculosis among, say, the Filipinos, Chinese and American Indians, whose consumption of cow's milk or its products is practically nil, will at once show how unwarranted is the contention. Cervical tuberculous lymphadenitis will be found to follow a curve that is expressive of at least three moulding forces. These are (1) the bacillary *milieu*,—whether human or bovine matters not at all; (2) the physical environment and habits of the recipients,—whether dirty or clean matters much; and (3) the anatomical character of the lymphatic system,—whether of a kind to ensure free or impeded entrance and conveyance of germs received matters decisively.

Accordingly, as a factor in the pathogenesis of tuberculosis, virulence of germ can be considered as momentous only within very broad limits, and for the infected individual hardly at all. It is when we come to quantitative fea-

tures of the parasite that we are especially impressed with the varying possibilities of effect that the germ is capable of.

Dosage of Bacilli, So-Called: For here we have real evidence that counts, difficult though it may be to place it aright in the scheme of human infections. Biological experimentation yields testimony too clearly and readily to doubt that so-called "dosage" of tubercle bacillus can be responsible for differences of anatomical result, and therefore perhaps in regard to human pathogenesis. Take the same germ, make a suspension of it, and inoculate variable amounts of this same suspension into series of susceptible animals by way of first infection, and you get wide differences of pathological and clinical effect. You will set up a range of infections from those that may not become manifest in months and years to those that kill in weeks. The certainty of activity of the infection, the rapidity of first appearance and later development of anatomical changes, and the vigor of morbid effects will all be directly proportional to the numbers of bacilli concerned in the initial experimental infection.

On this fact is erected the doctrine of so-called "massive" infection. It is (so it is held) when the quantities of bacilli received are large, rather than ordinary or small, that the resulting infection is likely to become pathogenic. There have been some writers who would apparently make this the most important pathogenetic factor concerned in tuberculous infection.

We would not question the soundness of the general proposition that size of "dosage" counts; we could bring forward numerous instances in support of it, especially in the case of metastatic reinfection. But, as to what extent "massive" dosage is operating to bring about that diversified evolution of infection that is so characteristic of tuberculosis in actual human life,—that is another matter, and for us the important one; and we might point out here the risks of error involved in explaining, without further analysis, too much connected with the subject on the basis of "massive" infection, if by "massive" we understand very large or exceptional quantities of bacilli received from without and proceeding to set up fresh foci within the body.

In the first place, it is only too common in actual practice to find, say, children frightfully exposed to tuberculosis and yet remain free from manifest disease, and frequent to meet with other children exhibiting clinical tuberculosis notwithstanding a contact that can be proved to have been slight, or too trivial to admit of substantiation. Lack of time prevents the documenting of this statement with particulars in support of it. But I am confident that any unbiased inquiry would bring to light compelling evidence of so many cases whose clinical course could not be correlated with determined "dosage" of initial infection that we would be obliged to relegate this particular factor to the background in numerous *particular* instances.

Again, we must ask ourselves whether we are clear as to what we mean by "massive infection" in actual

life and whether "massive infection," *as first infection from without,* is really taking place there. It is easy to conceive of metastatic reinfections as being "massive,"—such, for instance, as when large foci erupt and send their contents to places where at one given time the material is concentrated and brought to bear upon a small territory. In experiment too it is easy to place with a syringe large numbers of tubercle bacilli at a single depot within the body. But can similar conditions be satisfied in the act of natural infection from without? It is well known that before they can exert an anatomical effect tubercle bacilli *of first infection* must be carried past the integuments and be deposited within the body,—beneath the skin or mucous membranes. We may conceive of large numbers of germs, "massive doses," being inhaled or ingested at any one time. But can we imagine great quantities borne submucosally anywhere at a single point at one time?

There are on record instances of infants infected by phthisical rabbis in the act of ritual circumcision. These infants then went on uninterruptedly to progressive tuberculosis and death, as they exhibited an infection that was identical with that to be observed in the subcutaneously inoculated guinea pig. But, be it remembered, the conditions of infection were identical: here were cases of massive human infection, and no mistake. When Cornet exposed his guinea pigs to contaminated dust that he set in motion by sweeping, he arrived at disappointing results,—rather minimal infection, and confined to the tracheobronchial lymph nodes; as did Heymann when he had far-advanced tuberculosis patients cough for long and repeated periods into the faces of guinea pigs whose heads were fixed in direct line with the cougher and at a distance of only a few inches. The failures to produce anything but rather mild tuberculosis in guinea pigs by feeding them infected material are well known. Practically all inhalation and feeding experiments that have resulted in the familiar rather rapid and progressive tuberculosis of guinea pigs have involved conditions that must be considered highly artificial with reference to natural human infection, and such as we might call "strong-arm," to say the least. As conditions approached those which may be presumed to govern human infection, the results became more similar,—milder and more delayed manifestations, or even the absence of progressive tuberculosis.

Yet it can hardly be denied that, by and large, there is in human life a direct correlation between the quantitative factors of contact and the incidence of clinical tuberculosis, that is, pathogenesis. Any inquiry into pathogenesis must attempt to explain why, for instance, the children of tuberculous homes and those of tuberculous parentage will break down with tuberculosis with inordinate frequency.

We cannot speak with certainty here. There is the economic factor to be considered,—the circumstance that, in general, tuberculous infection, subjected to the stresses and deprivations that reduced pecuniary resources entail, responds toward activity: and few diseases can, and more commonly do, make greater financial wreck of a

home than tuberculosis. There is, again, the constitutional factor to think of. About this, as has been shown, we have no real information. Nevertheless, as has been said above, all that we know about *specific* immunity would suggest that, if anything is inherited in this respect, the repeated tuberculization of the generations of a family should result in increase of immunity rather than its opposite.

We suspect that, if we could get at the truth, we should find that what is most effective in bacillary contact, quantitatively considered, are opportunities for repetition of infection, and particularly the intervals of time between repeated infections. Experimental work, which would take too long to relate, suggests this strongly, and in summary leads to an opinion something as follows: A prolonged and more or less continuous exposure to tuberculosis, with its chances for frequently repeated intakes of bacilli, and especially as intervals between successive infections become shortened, is decidedly more momentous as to pathogenesis than single casual or occasional contacts, no matter what the dosage.

Conclusion

As we follow the many varied threads of this complicated and tangled skein that leads to the pathogenesis of tuberculosis, we should ever keep in mind that between the time of reception of offending bacilli and that of pathogenesis the natural history of tuberculous infection rarely discloses it as pursuing an uninterrupted course. Even *infected* infants who do fall ill (and only the lesser number do) will be found to go weeks and months with inactive infection before breakdown; the child months and years; the adult years and decades. If we had no other facts to guide us, this circumstance alone should teach us that, in the majority of cases, neither native character of tissue nor kind or "dosage" of bacillus is decisive in establishing the pathogenesis of tuberculosis, contributory though each may be to the end-result. The net result of this inquiry is to suggest that, in most cases, out of the first meeting of virulent germ and susceptible host, there results a tissue graft which, placed in the tissues of the animal, man, living a normal existence, would, because of a prompt acquisition of allergy and immunity, go the way of limited development and at last obsolescence. But civilized man has drifted far from the life of man the animal, and in the journey has been and is subjecting his engrafted tubercle to varied forces that promote its growth and spread. Back of every awakening of tubercle, back of every nurturing of its evolution, is an experience or succession of experiences that have promoted its continued existence and progression. Common observation teaches us that, regarded physiologically, such an experience is characteristically of a stressful nature. Whatever may be stressful is to be viewed in its relations to the individual. The ultimate solution of the problem of pathogenesis of tuberculosis in human beings must be sought where the sick human being is,—in the clinic,—and the answer read out of the story of the human being himself. And, so far, his imperfect accents all speak one way,—to the effect that it is what he has done

and what has happened to him since infection that have been most momentous. Environment, individual experience, has swung toward or away from pathogenesis the balance fixed by initial meeting of germ and host, and soon affected by allergy and immunity.

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Pulmonary Tuberculosis*

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Infection

ADULT ulcerative pulmonary tuberculosis exemplifies the achievement of the life cycle of the human tubercle bacillus. Egress of the parasite is now accomplished so that it is free to attack other victims. It has been long recognized that adult pulmonary tuberculosis is a reinfection of a patient previously infected and partly immune; but whether such reinfection is endogenous or exogenous is a topic extensively debated. Bushnell published many arguments in favor of endogenous reinfection, basing them on the well known Koch phenomenon by which it is demonstrated experimentally that an infected animal, though it goes on to die of the primary tuberculosis can yet resist large numbers of tubercle bacilli given at a second injection. Bushnell considered that there were two kinds of infection in tuberculosis, bacillary infection, and bacillary infection fortified by the accumulation of toxic substances. There should therefore be two kinds of immunity, otherwise no caseated focus could fail to be fatal. According to Bushnell therefore, adult pulmonary tuberculosis was due to a second infection from within and this second infection spread from an original infection by virtue of accumulated toxic products together with the bacilli. Experimental work on laboratory animals has shown how distant lymphatic structures become infected following inoculation of tubercle bacilli. Many bacilli are filtered through the lungs and pass to the lymph structures at the bronchial bifurcations and to the tracheo-bronchial nodes.

Such bacilli may die out, or hibernate, and it is conceivable that latent bacilli at the bifurcations of the bronchi or in the tracheo-bronchial nodes, may rekindle and develop into active pulmonary disease many years after the original infection. In recent years Opie has claimed that adult pulmonary tuberculosis is due to a reinfection from without. Opie bases his statements on careful autopsy work and X-ray studies. He has found that in conducting autopsies on those who have died of diseases other than tuberculosis, guinea pig inoculation will reveal tubercle bacilli in the lung apices of thirty per cent of the subjects; he found them often in apparently normal lung tissue and interprets this as showing their frequent presence in the inspired air. Opie also found that in families where the husband had active

*Presented to the American College of Physicians at the Annual Clinical Meeting in New Orleans, March 6, 1928.

pulmonary tuberculosis the same disease existed in fifty per cent of the consorts studied. While marital disease may be thus frequent in the poor it certainly does not exist in such high ratio in the well to do, whose hygiene and living conditions give better protection.

It seems to me there is an important difficulty in accepting the exogenous theory of reinfection, and that is, that it credits the tubercle bacillus with having evolved an entirely anomalous life history unlike that of any other parasite known to us. That is to say, the theory assumes that the tubercle bacillus after creating a primary lesion in a young person must lie dormant for one or several decades awaiting another independent invasion by a new lot of bacilli to complete its life cycle by means of an open ulcerative process. Even so the original invaders are doomed to extinction. In the case of any other known parasites the cycle if completed at all is completed by the progeny of the original invaders.

The finding of tubercle bacilli in the lung apices of thirty per cent of non-tuberculous autopsies would suggest that the bodies were immune to attack by these organisms, and at the same time their presence might indicate that most of us are constantly in jeopardy of a second attack. The fact that the tubercle bacillus is so ubiquitous might favor a second exogenous attack. The importance of the subject enters social medicine for it has been the teaching, as an offset to phthisiophobia, that in general, adults are not endangered by ordinary contact with a consumptive. Clinically we see tubercle at the apex of one lung spread to the other lung when the patient has no sputum, and has not been in contact with another patient with this disease. We are all familiar with the manner in which lipiodol may be sprayed through the bronchi, following a cough, in patients who have been instilled with this oil. It is easy therefore to visualize how sputum may be scattered in the lungs following cough. It may be that small amounts of sputum which are not enough to produce a cough may be good culture media for the tubercle bacillus, and that insignificant amounts of sputum may be occasionally sprayed into the other lung in throat clearing or slight cough. Theobald Smith believes this to be a reasonable conjecture. On the other hand extension in these cases may be circulatory, especially lymphatic.

It is possible that pulmonary tuberculosis may be the outcome of either exogenous or endogenous reinfection but until more proof is forthcoming it is not an unreasonable deduction to credit the latter with the more important rôle.

Treatment

No specific having been discovered as a remedy for pulmonary tuberculosis we have seen the development of the valuable principle of rest by the perfecting of artificial pneumothorax; and more recently, in carefully selected patients, the methods of surgical lung collapse. Some years ago, however, we advocated what we termed postural rest and in bilateral apical and other lesions the application of shot bags. The endorsement of these principles by Pratt and more recently Gekler,

encourages me to speak to you in more detail concerning them. We noticed that patients with activity in one lung were apt to rest on the side which was little or not at all diseased. Investigation of normal subjects taught us that when a person lies on one side the dependent lung is placed at rest. Not only is there little aeration in this dependent lung but the heart and mediastinum incline to this side and the increased motion of the diaphragm which at first takes place is soon reduced and the dependent half of the diaphragm assumes a relatively higher position. If X-ray films are taken of a normal subject who has spent a half hour lying on one side it will be noted that the above phenomena occur and there is much less penetration of the lung by the rays. In some subjects the lung area appears reduced by nearly a half. We advised the placing of a small hair pillow under the recumbent side to decrease the motion and to add to the patient's comfort. With careful nursing a patient can rest on one side many hours a day for weeks at a time. For drainage we advise patients undergoing postural rest treatment to turn on to the side of the more healthy lung several times a day for some ten minutes or more in order to expel sputa with the aid of gravity. We have found that in hemorrhage postural rest may aggravate such a complication and when this occurs the patient is placed on the back and a shot bag applied to the lung apex. The application of shot bags is the best means we have for patients with bilateral apical activity. Special bags are made which measure five inches square; in these four rows of medium shot are placed in a series of compartments like those of a cartridge belt, but securely stitched on all sides, the total weight being about a pound and a half. The bags are sewn across in four or more compartments and one of these is filled with shot each day until the bag is complete. The application of such shot bags over the upper lobes of the lungs results in lessened thoracic and increased diaphragmatic breathing. Since our first publication the use of shot bags has grown more and more in favour with our patients and they have appreciated the acceleration of the arrest of activity in their lungs. The placing of a shot bag over the upper part of the chest of a patient with pulmonary hemorrhage is one of the best methods of treatment for this complication.

I have called attention before to the fact that we as physicians have not been thorough in resting the lungs of our patients who have pulmonary tuberculosis. Respiration takes place over one thousand times an hour in a normal person. Our surgical colleagues have been much more thorough in carrying out rest of tuberculous joints. They do not take off splints directly symptoms subside and it is a great mistake for physicians to allow patients to get up when temperature, pulse and sputum have subsided. The best result I have ever obtained in pulmonary tuberculosis was in a young man who insisted on staying in bed for eight months after I had advised him to get up and begin exercise.

Lantern slides are shown which indicate that tubercle deposits in the lungs and even cavities may entirely disappear, but to achieve these results an average of two years rest in bed has been necessary.

Intestinal Tuberculosis*

By Robert S. Berghoff, M.D., F.A.C.P., *Chicago, Illinois*

Intestinal Tuberculosis

I

THE subject of intestinal tuberculosis is of practical importance for several reasons. In the first place, because of its great frequency, it is present in probably fifty per cent of all cases of far advanced pulmonary tuberculosis. In the second place, because the symptoms are atypical, sometimes unbelievably masked, and in consequence render an early diagnosis difficult. First a few statements relative to the origin and mechanism.

Intestinal tuberculosis is practically always secondary to a lung infection, very rarely indeed is it primary. That this is so, has been and can be demonstrated at autopsy by a study of the regional mesenteric lymph glands. Numerous workers (Furst, Carr, Woodhead and others) have shown the relative frequency of undoubted primary mesenteric gland tuberculosis, with not a trace of tuberculosis in the intestinal wall. Bacilli can and do pass through the walls of the intestinal tract without leaving a trace, and once through the mucous membranes, are carried to the mesenteric glands, or may be carried with the chyle to the thoracic duct, and then into the blood stream (1). This procedure is the very antithesis of the primary infection of childhood. In the primary infection, the tubercle is inhaled, passes down the bronchus and lodges in an alveolus. Tubercle bacilli multiply and a tubercle is formed. This tubercle caseates, and because lung tissue possesses no specific defense, it must rely upon the lymphatics. The regional lymph glands then take part and scavengerize and encapsulate within their parenchyma the tubercle bacillus and detritus from the lung. This process is the so-called Primary Complex of Ghon. So surely and constantly is this the mechanism in the primary infection, that to find at autopsy in the juvenile lung the primary tubercle, it is only necessary to find the infected regional lymph gland. If the caseated lymph gland belongs to the peribronchial chain, then will the tubercle be found in the base of the lung, or again, should the caseated lymph gland belong to the peritracheal chain, then will the primary lung tubercle be found in the upper lobe.

Pathology. The pathology of tuberculosis irrespective of where encountered or what organ or structure involved, is of course basically the same, and consists of the tubercle. In the intestinal tract however, the tubercle shows a tendency to rapid and

*Read before the American College of Physicians, New Orleans, March 6, 1928.

wide-spread disintegration with resultant ulcer formation. It is encountered most frequently in the ileum and caecum. Peyer's Patches are a common location as in typhoid fever. However the tuberculous ulcer shows many striking differences from the typhoid. In the first place, it is almost always multiple, in contrast to the not infrequent solitary ulcer seen in typhoid fever. Next, it spreads transversely around the gut, often completely encircling it, instead of following a longitudinal path as in typhoid, the reason being the circular direction of the lymphatics by which it spreads. A typhoid ulcer is prone to rapid perforation, the tuberculous ulcer perforates infrequently, the reason being, a greater tendency to granulation thickening and new tissue formation. The walls and edges are thickened and raised, but not undermined as in typhoid. The floor is caseous and often shows miliary tubercles. As a rule all coats of the intestine are involved, including the serous which leads to adhesions and peritonitis. The end result of a tuberculous ulcer may be two-fold: 1. If the anabolic process, new tissue formation is in the ascendancy, a stricture of the bowel will result, or 2. If catabolic, then necrosis, caseation and ulceration ensue.

Predisposing Factors Towards Intestinal Tuberculosis

What factor or factors are instrumental in the origin of an intestinal infection? Constipation with its associated stagnation is unquestionably one of the foremost. This I believe is demonstrated by the fact that the disease is most common in the so-called "Sluggish Areas," the lower ileum, cecum, and ascending colon. Bacilli require and are provided with prolonged contact and thus produce infection. 2. The absorptive activity of the gut is possibly another factor, for the ileum, cecum and asceding colon in that order boast of most rapid absorption. 3. A pre-existing colitis, dysentery or previous typhoid fever by their undermining influence and local trauma, are also factors. 4. Trophic changes in the intestinal wall due to prolonged toxemia of a co-existing lung tuberculosis must be considered.

Symptoms: The symptoms of tuberculous enteritis are not alone extremely variable, but are often amazingly meager. History, symptomatology, physical findings, and the character of the stool collectively and individually offer an atypical picture, and what is more surprising, is the practical absence of any sign except possibly an alternating constipation and diarrhea, in the presence of pronounced enteritis. However the following symptoms because of their relative constancy, merit special attention: 1. Constipation and diarrhea. The former as encountered in that group in which the pathology leans towards cicatrization and stricture of the gut. This stricture of the bowel is of two types: In one there is a general lymphatic process. The walls of the intestine are thickened uniformly, and the lumen reduced to a very small caliber. The other type is that which follows ulceration. The edges and bases of the ulcer thicken and later contract, encroaching upon the lumen. Rarely is there complete obstruction,

although clinically, the obstipation may be intense. Diarrhea is periodical with spontaneous remissions. The stools are in no way characteristic. They may be thin and watery with much poorly digested food material. Or again they may be soft, mushy and of foul odor, and mixed with blood. Almost always they contain mucous and tissue shreds. Nocturnal stools are probably more frequent than in any other type of dysentery. Tubercle bacilli are practically constant, but this has no diagnostic significance, for as Pottenger (2) aptly remarks, they are to be found in the stools of nearly every individual who has a positive sputum. Mere frequency fo stools is no indication of the existence of a specific enteritis, since the same thing ensues in the catarrhal inflammatory process often present in a chronic toxemia like pulmonary tuberculosis.

2. *Pain*:—is a most uncertain symptom in tuberculosis of the intestine and is certainly no index as to the severity of the infection. The most marked invasion of the intestinal tract sometimes apparently causes little or no distress. When present, pain is most variable. If colicky in character, it probably speaks for an obstructive type of lesion. It may be a diffuse constant soreness throughout the abdomen, or again a tenderness on pressure only. In such cases, the tenderness is often most pronounced over the cecum or at least in the right quadrant. It is not unusual however to encounter a referred tenderness over the entire abdomen. Changes in motility—intestinal ulceration of any variety and tuberculous included, influence the motility of the gut. Accordingly we have periods of dysentery succeeded by severest constipation, and vice versa.

3. *Stomach symptoms*:—are fairly constant, appear early, and prove annoying. They are essentially absolute loss of appetite, with a disgust for food and nausea; vomiting is not frequently encountered. The effect on nutrition is evident. There is progressive loss of weight, which may lead to extreme emaciation and cachexia. Even in the absence of stomach symptoms, there is difficulty in keeping the patient nourished.

4. *General Symptoms*: The temperature in intestinal tuberculosis is in no wise characteristic, and is the same as in tuberculosis anywhere. It is however a rough index as to the degree or severity of the invasion. It is also true that during the stage of ulcer formation, the temperature remains high. There are some who claim for intestinal tuberculosis pronounced slowing of the pulse and thereby a disproportion between pulse and temperature, due, it is asserted, to an inhibiting action of the vagus. I have never found it so.

5. Muscle spasm, is certainly encountered as a rule in intestinal tuberculosis. It has a definite diagnostic but scarcely a differential diagnostic value. Pottenger (2), insists there is frequently a selective or localized spasm of true diagnostic import, for example, a rigidity over the ileum or cecum or ascending colon depending upon the location of the underlying ulcer.

6. Hemorrhage of considerable degree is an uncommon finding in intestinal tuberculosis. It does occur and sometimes fatally so, but it is the big exception. The reason being that the pathological process in the bowel tends to obliteration of the vessel before ulceration occurs, much the same as in lung tuberculosis.

Differential Diagnosis: Only frequent encounter with intestinal tuberculosis impresses one with the complexity of the diagnosis. At first thought it would seem that there should be no confusion, no great difficulty in differentiating a specific invasion of the bowel, from other common forms of dysentery. At times the detection of intestinal tuberculosis is difficult. In the first place, while it is usually associated with advanced pulmonary tuberculosis, it is by no means restricted to this stage. It can and does occur as a complication in an early stage of the disease, when even the primary infection is none too frank. In such cases, intestinal tuberculosis is differentiated with difficulty from: (a) amebic dysentery, (b) mucous colitis, (c) malignancy of the bowel. From amebic dysentery the diagnosis must be arrived at by the history, absence of ameba, and presence of tubercle bacilli. So far as the physical properties of the stools are concerned, they may be identical. Mucous colitis may present a picture so similar, that only unmistakable evidence of clinical pulmonary tuberculosis and the presence of tubercle bacilli in the stools will render a diagnosis. It is in the third group however, malignancy of the bowel, that the greatest difficulty is encountered. We all appreciate that while a carcinoma of the bowel through stricture causes obstipation, it not infrequently is responsible for the opposite, a diarrhea. When this symptom maintains, the differentiation from tuberculosis is difficult indeed. It can often be made only by finding the tubercle bacillus in the stool. The clinical picture is most similar. The same strain of gastro-intestinal symptoms, nausea, anorexia, disgust for solid food, the same colicky pains in the abdomen, and diffuse tenderness on pressure. Slow but progressive loss of weight on a diet of sufficient caloric intake is encountered in both, as also a cachectic appearance and an associated secondary anemia. In far advanced active pulmonary tuberculosis with a positive sputum, when the diagnosis is certain, there is often question as to the nature of a co-existing dysentery. A high percentage of all individuals with an advanced lung tuberculosis develop during the course of their disease a catarrhal inflammatory process of the intestinal tract due to trophic or mechanical irritation which in every respect resembles a true tuberculous enteritis: pain, tenderness, frequent stools containing blood, mucous and tubercle bacilli, and yet no ulcer formation in the bowel. The diagnosis is only arrived at after careful patient observation.

Sequelae and Complications

1. Perforation and peritonitis are uncommon, due chiefly to the rapid formation of granulation tissue which accompanies the destructive ulcerative process. However, when the serous

coat of the bowel is involved, a generalized peritonitis can and does occur.

2. Localized abscess formation (cold abscess) which follows perforation. Such a walled-off abscess may be easily confused with ileo-cecal tumors and appendiceal abscesses.

3. Stenosis of the intestine—due to cicatrization of a healing ulcer, is not infrequent. The stenosis as a rule, is not absolute, but remains a definite narrowing.

4. Tuberculosis of the mesenteric glands and of the peritoneum by contiguity, i.e., direct spread, is frequent. It is probable that we do not appreciate how frequently tuberculosis peritonitis is the direct result from a specific lesion in the bowel, invading its outer serous coat. It is true direct extension from the chest via the diaphragm is one big source, or transmission from the uterus by means of the fimbriated ends of the tubes another. However, tuberculous enteritis surely forms the atrium in considerable instances.

The pathology consists essentially of a chronic proliferative process involving chiefly the muscular and subserous coats. It results in a tremendous thickening of these coats, and a consequent narrowing of the lumen, often to pencil size. It is usually of one or two types: I. A localized definite tumor in the right iliac fossa which is hard, fixed and tender. 2. A generalized thickening without definite tumor. This type is often associated with a fecal fistula.

Symptoms:—consist of attacks of pain in the right iliac fossa, alternating diarrhea and constipation, rigidity of overlying muscles, tenderness either localized or diffuse, and general body wasting.

Differential Diagnosis: 1. From cancer it is difficult, since the symptomatology and findings are the same, and the stools rarely show bacilli. 2. From appendicitis, chiefly through chronicity. The treatment is surgical and consists in lateral anastomosis with removal of the tumor.

Prognosis: Tuberculous enteritis is not necessarily fatal, for both the ulcerative and the proliferative types are often self-limited and heal. When however, in the ulcerative type the infection of the intestinal wall is diffuse and wide-spread, the outlook is bad. There is no question but that the prognosis of intestinal tuberculosis has brightened perceptibly in the past two decades, and more especially in the last ten years. The texts of thirty years ago, and even more recent ones, considered intestinal tuberculosis a hopeless, fatal complication, with only an exceptional cure. Our entire attitude in this regard has changed, and marked improvement and undeniable cures are quite frequent. The reason is two-fold: 1. An earlier diagnosis. 2. The addition of therapeutic measures of real value, one in particular, artificial heliotherapy, to be discussed under Treatment.

Treatment: Let us consider first, briefly, the surgical possibilities for the relief, arrestment and cure of tuberculous enteritis. The obstacles and handicaps are apparent at once, and are as follows:

1. The early symptoms and objective signs are vague, and in consequence the diagnosis is in most instances not made until the pathological process has made extensive headway. We are then dealing no longer with a local circumscribed condition.

2. The patient has become so devitalized by a ravaging long-drawn out lung tuberculosis, that he is unable to meet operative interference. Surgery is indicated and accompanied with satisfactory results in the following cases:

1. In the ulcerative type, if the infection is confined to the cecum or portion of the ileum. The removal of the infected parts leads to improvement, provided further infection in other portions of the intestinal tract does not occur, which unfortunately is the rule.

2. In the chronic hyperplastic type previously discussed, the results are sometimes excellent, again provided the patient's general condition will tolerate the insult.

In taking up the general non-surgical treatment of intestinal tuberculosis, it might be well to preface with the statement that the treatment of tuberculosis anywhere in the body is much the same, and has to do with the development of immunity by bringing the health, strength and resistance to as high a level as possible. The first measure and probably the most important, is rest.

Rest:—is essential and indispensable in the cure of tuberculosis of any variety, and it is a fact which even today is quite apparently not fully appreciated. Rest is immunity's greatest synergist, and it must be as absolute as possible. There is probably no other factor of equal importance. In intestinal tuberculosis, rest is invaluable and must include:

1. General rest.
2. Local rest.

By general rest we mean absolute rest in bed 24 hours out of 24. To temporize and allow a patient any leeway in this respect, is tragedy. Not only is general strength conserved through a diminished demand on vital capacity, but what is equally important, peristalsis is thereby retarded, for exercise calls for increased motility.

Local rest: or retarded peristalsis, is accomplished by the following measures:

1. Diet: which in tuberculous enteritis is a very complex problem. Obviously it will vary depending upon the presence of a diarrhea or constipation. However, in either, it must at all times be bland and non-irritating, and above all highly nutritious, since the maintenance of the patient's strength is after all the real criterion. In the presence of a diarrhea, not only irritants but stimulating foods as well are contra-indicated. Fruits and vegetables which form the bulk of an average diet, and which because of their nourishing qualities and vitamine content are important to the tuberculous, must be kept at a minimum, because of their stimulating action on peristalsis. Sweets fall into the same category. The coarse so-called "Roughage Foods" are undesirable for their dual stimulating and irritating effect. Meat extracts and red meat are stimulating to peristalsis and are to be al-

lowed only guardedly. It will be seen therefore that an ideal diet is hard to attain and still more difficult to maintain. In addition we have to deal with a jaded, capricious appetite in an individual who must be nourished, and unfortunately must be humored even to the point of allowing foods which are illogical.

The diet in a period of constipation is not so restricted. However, here too we are handicapped in our reluctance to push the foods which by their peristaltic stimulation would accomplish a desired end. Remembering that most of these foods stimulate by irritating, a conservative judgment is therefore called for in the dietary management of tuberculous enteritis.

In addition to rest and diet, other methods of combating diarrhea which deserve mention are: Local heat to the abdomen. Experience has proven that moist heat is desirable, and is probably most effective in the form of moist packs. Hot cloths changed every twenty minutes for several hours each day, and covered with dry ones or with oiled silk, if practical. 2. Hot bland enemas if given cautiously afford relief, but their daily use is not advisable. Starch or bismuth may be added, but as for the nitrate of silver or any other astringent, I personally have always lacked courage. 3. Remedies by mouth are of course numerous, too many to mention in detail. Some have real value especially in mild cases, and exert no apparent harmful effects. In a severe form, they are not only dangerous, but usually ineffective. Drugs commonly used and which possess merit are: 1. Atropine in the form of the sulphate given in conservative doses (1-200 grain) relaxes an existing spasm. 2. Bismuth subnitrate in 30 grain doses, suspended in water, and repeated twice in twenty-four hours is harmless and effective. 3. Calcium carbonate and phosphate in large doses of each 30 grains, three doses in 24 hours may be tried. 4. When we come to the subject of opium and its derivatives, it is most difficult to advise or lay down a rule. Surely in mild early cases, they are contra-indicated. In the severe forms, when all other remedies fail, what recourse have we? The deodorized tincture is probably the choice. It is borne well, causes less nausea, and is discontinued with less difficulty than most other forms. The dosage will vary with most individuals with a range from five minims three times daily, to twenty.

X-ray and Heliotherapy:—constitute a therapeutic contribution of the past decade, and they are a real substantial addition. The form of choice is the ultra-violet ray. It must be given intensively (ten minute exposures) at a distance of from 10 to 14 inches, and over a long period, months beyond the disappearance of clinical symptoms.

Tuberculins: On no phase of the treatment of tuberculosis do we encounter a wider divergence of opinion than in the use of tuberculins. This is due to the difference of results obtained by individual men. In German countries, especially Germany and Austria, they are popular. Newman of Vienna for example, is enthusiastic.

1 and 2: POTTENGER—Clinical Tuberculosis, Vol. 1, 2.

The Response of Chronic Nephrosis to Parathyroid and Thyroid Medication*

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THE question of the classification of disease is always a contentious one, and this is particularly the case in diseases of the kidney. The very number of these classifications is the best evidence of their unsatisfactory character, yet constant progress is being made in the correlation of the clinical picture with the pathological findings. With increasing knowledge, more definite clinical entities are being built up, and there is now a reasonable arrangement of the types of renal disease in which hypertension, cardio-vascular changes and nitrogen retention are outstanding features. However, in those cases in which edema of so-called renal origin is present, it has only been comparatively recently that extended chemical studies have enabled a more clearly cut grouping of allied lesions, which might be dignified by the application to them of definite names.

Amongst these more recent groups may be mentioned the nephroses, a type of kidney lesion in which degeneration rather than inflammation is the outstanding feature. The term was introduced by Miller (1) in 1905 to describe a condition in which there is marked degeneration of the tubules, while the glomeruli are involved to a very slight degree, the glomerular damage being secondary to that in the tubules. This condition is in strong contrast to that seen in the inflammatory lesions, where the tubular damage is secondary to that in the glomeruli. Since that time this broad group has been subdivided, so that at present the term "chronic nephrosis" is applied to a comparatively restricted number of cases having a fairly typical clinical picture.

Munk (2) in 1913 first drew attention to a group of cases in which albuminuria, edema, and low blood pressure were associated with the passage of doubly refractile lipoids in the urine and the presence of these same lipoids in the cells of the convoluted tubules of the kidney. About the same time Epstein (3) began his observations on certain cases of "chronic parenchymatous nephritis" which showed a reduction in the total plasma proteins and a reversal of the albumin globulin ratio of the protein constituents of the blood. Munk applied the name "Lipoid Nephrosis" to his cases, while Epstein used the term "Chronic Nephrosis." Murphy and Warfield

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(4) in an excellent résumé point out that these descriptions are of the same disease viewed from different chemical angles. Volhard and Fahr (5) also present one group of their nephroses —the genuine nephrosis—in which lipoid degeneration is a characteristic feature.

The existence of a clinical entity, chronic or lipoid nephrosis, therefore, may be conceded, but when the true nature of this disturbance is enquired into, the causes of the lipoid degeneration and an explanation of the clinical characteristics of the disease, one immediately meets with conflicting statements. Is the disease to be regarded as being of renal origin, or are the kidney lesions secondary to some general disturbance of metabolism? The answer to this question is still uncertain. Eppinger (6), Kollert (7), and Epstein (8) suggest a general metabolic disturbance, with the renal lesions resulting from the passage through the tubule cells of certain irritating substances arising from this disturbance of metabolism. Eppinger (6) and Epstein (8) both believe the condition arises from an endocrine insufficiency, and the latter puts forward a new name—"Diabetes Albuminuricus"—to divorce our minds from the conception of its being primarily a renal disease. In support of this theory of endocrine origin, one may refer to the lowered basal metabolism shown by many of these patients, and associated with this lowered rate there is a marked increase in the lipoid content of the body, particularly in the cholesterol fraction. Again, the disturbance of the plasma proteins suggests some general disorder rather than a purely renal damage. Finally, the therapeutic test of certain glandular products (thyroid and parathyroid extract) gives strong evidence for the endocrine causation of the disease picture.

The frequency of the pure lipoid nephrosis is not great, but careful chemical studies tend to identify it much more often than would be expected. On the other hand mixed forms, nephrosis grafted upon a chronic glomerulonephritis, or an initial lipoid nephrosis with a complicating nephritis, are relatively common occurrences. It is these mixed forms which give the persistent edema and marked albuminuria associated with an increased blood pressure, red blood cells in the urine, or nitrogen retention, none of which are seen in the pure chronic nephrosis. So often is this mixed form present, that Kollert (7) states that a mild glomerulonephritis is a necessary antecedent of nephrosis, and that so-called pure chronic nephrosis only occurs when this glomerulonephritis is so slight that it escapes detection.

The Clinical Picture of Chronic Nephrosis

The pure lipoid nephrosis (Munk) or chronic nephrosis (Epstein) is characterized by an insidious onset, and rarely is there any history of a preceding acute infection. Edema is the first symptom, and is of the renal type, collecting under the eyes, or in the loose tissues about the ankles. The edema gradually increases, transudates develop, and these collections of edema prove extremely resistant to

the ordinary methods of treatment. The skin takes on an extreme pallor which is quite out of proportion to the blood count. The volume of urine is decreased, but its colour is not changed. The cardiovascular system escapes completely, the blood pressure is not raised, and the vessels are not thickened. The eye grounds are normal and the Wassermann test negative. The urine has a moderately increased specific gravity, but the outstanding feature is the large amount of albumin, 10 to 20 grammes to the litre not being unusual. The sediment varies considerably, casts are not numerous; there may be considerable numbers of leucocytes, but red blood cells are absent. Under the polarizing microscope double refractive fat droplets are conspicuous, both floating freely and in the casts.

Blood Chemistry

The blood urea and other non-protein nitrogenous constituents rarely show any change, although they may be increased slightly when the edema fluid is being excreted. The cholesterol is much higher than usual; instead of the normal value of 180 mgms. per cent, readings of from 600 to 800 mgms. are not infrequent. The blood calcium tends to be depressed, and values of from 5 to 7.5 mgms. per cent are commonly found instead of the normal 10 mgms. per 100 c.c. Epstein's chief contribution to the chemistry of the disease is the alteration in the plasma proteins. According to Linder, Lundsgaard and Van Slyke (9), these normally vary between 6.22 and 7.45 per cent, with a ratio of 1.6:1 between the albumin and globulin fractions. In cases of nephrosis the plasma proteins are greatly decreased. This decrease is largely at the expense of the albumin fraction, the globulin fraction being almost unchanged. The result is a relative increase in the globulin, and a reversal of the albumin globulin ratio. Much stress has been laid on this lowering of the plasma colloids, as a possible explanation of the edema which is such an outstanding feature in these patients. Govaerts (10) points out in addition a lowered osmotic pressure even below that which would be expected from the low protein content in certain cases of edema, and this coincides with Clausen's (11) suggestion that some toxic material is present which increases the permeability of the cell membranes and consequently tends to increase the edema. Mason's (12) report would tend to strengthen the position of those who claim that disturbance of the colloids is not the sole factor in the collection or dispersal of the edema, as his case showed over a period of months that plasma protein concentration and reversal of the albumin globulin ratio had little, if any, relation to the degree of edema. Some other factor must also be at work.

Endocrine Features of the Disease

As mentioned above, there are definite disturbances of the endocrine system, one feature of which is the frequent lowering of the metabolic rate. Even after correction for the false weight due to the edema, values of from 15 to 20 per cent below normal are not uncommon. The marked improvement shown after thyroid medication would indicate a particular in-

volvement of that gland. As Epstein (8) points out, many of these patients show an extreme tolerance for thyroxin, and large doses are required to produce definite effects. Again Davidson (13) notes the improvement appearing after parathyroid extract injections, in certain cases with a low blood calcium, while Guy Laroche (14) suggests a possible relationship between the adrenals and the high cholesterol values.

Another indirect feature having to do with the basal metabolism is the well-known fact that any intercurrent infection with high fever and a consequent rise in the metabolism is followed in these cases by the prompt disappearance of an edema which previously had resisted the ordinary methods of treatment.

Progress of Chronic Nephrosis

The general impression gained from the reported cases of chronic nephrosis is that the disease is not a rapidly fatal one, and that, once the edema is controlled, the patient is capable of a fairly active existence. There are many who do not share this belief. Kaufman and Mason (15) report a case which went into an early termination, and even in those that at first appear to react favourably there is often an increased susceptibility to infection, particularly to the pneumococcus. These infections materially shorten the expectation of life. In others, clinical evidences of contracted kidney slowly appear, and at autopsy the kidneys show advanced degeneration and shrinkage, but with very little evidence of inflammation, the so-called nephrotic contracted kidney.

It is possible that the rapidly advancing cases have been mixed types, nephrosis and nephritis, and that pure lipoid or chronic nephrosis is of a relatively benign character.

With these features in mind, certain illustrative cases may be presented, four in all, only one of which conforms to the criteria of pure chronic nephrosis, the others being mixed cases of chronic nephrosis and chronic glomerulonephritis.

Case No. 1: Mrs. B. H., aged 33 years. Admitted October 1925. The patient stated that for the past 5 years there had been recurring periods of edema. At first this had been chiefly about the ankles and under the eyes, but later it had become very considerable in amount, and had been sufficient to interfere with breathing. There was no history of any recent infection, but she had had rheumatic fever at 5 and dysentery at 25 years. At the onset there was slight frequency of urination, but later this disappeared. Restriction of salt and water intake, low protein diets, etc. had given no relief. Very small doses of thyroid had been followed by unfavourable symptoms, and were discontinued. Of interest from the endocrine standpoint was a sudden increase in weight after marriage. She had never been pregnant.

Physical Examination: Temperature, pulse and respirations were normal. There was marked general anasarca, and very definite pallor. No foci of infection could be made out. The lungs were clear; the heart was slightly enlarged and showed a mitral endocarditis with a moderate grade of stenosis. The vessels were not thick-

ened and the blood pressure was 140/80. The abdomen showed considerable free fluid, but the liver and spleen were not enlarged. The urine was acid, the specific gravity varied between 1016 and 1022, the albumin was constantly between 5 and 8 grammes per litre. Many casts were found, but no red blood cells.

The blood Wassermann was negative, and beyond a slight tortuosity of the vessels the fundi were negative. The blood count showed a moderate secondary anemia, with 4,480,000 red blood cells, 9,800 white blood cells, and 72 per cent hemoglobin. The blood urea and creatinine were within normal limits, but the urea concentration factor showed a definite impairment of renal function. The serum calcium was 7.1 mgms. per cent (normal 10 mgms.). The total plasma proteins were depressed, 4.4 per cent as compared with the normal of 6.22 to 7.45 per cent, and the albumin globulin ratio was 1:1.37 instead of the normal 1.6:1. The basal metabolic rate was plus 3 per cent.

Clinical Course: Marked salt and water restriction had no effect upon the edema. The usual diuretics gave no result. Novasurol (Merbaphen) was given, but after the second dose a severe stomatitis appeared, there was no diuresis, and its further use was stopped. Thyroid medication had not been successful before admission, its use having been followed by signs of hyperthyroidism. Owing to the kindness of Professor Collip a quantity of parathyroid extract was available, and in view of the low calcium, it was decided to ascertain the effect of raising the blood calcium. Accordingly, 50 units were given daily for 12 days, and 100 units on another day, and the calcium determined 12 hours after each injection. The calcium rose to normal (see Chart No. 1) and remained so during the period of injection; at the same time there was a marked diuresis, the output rising from an average level of 500 c.c. to 3,000 c.c. on the tenth day after the extract had been commenced. The edema rapidly decreased, and the weight fell 9 kilos in thirteen days. With the discontinuance of the parathyroid injections, the loss of weight stopped and a short time later a further series of six injections did not produce any marked loss of weight, possibly because the patient was almost free of edema.

After the second series of injections, an attempt was made to raise the blood calcium by exposures to ultra-violet light, but while the calcium values were kept between 8 and 9 mgms. per cent there was no diuretic response. Parathyroid preparations by mouth had no effect on the urine volume or serum calcium. During this period the edema collected rapidly, and a third series of injections of parathyroid was given, and in addition a daily dose of calcium chloride by mouth. There was a prompt rise in the calcium values (9 to 10 mgms. per cent), the diuresis returned and the edema disappeared. After this series the dose was gradually reduced, first to 25 units daily, and then to 25 units twice a week. This amount of extract sufficed to keep the weight curve constant.

At this point the patient refused to remain in the hospital. She returned

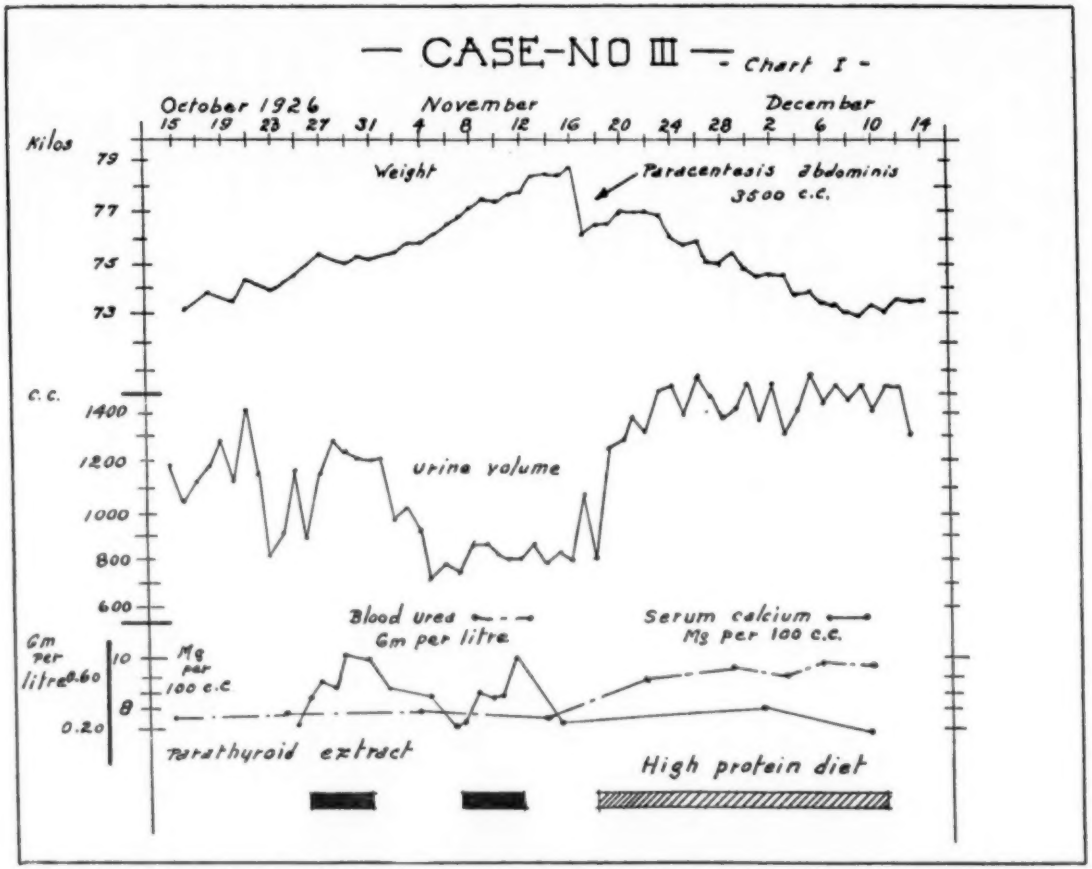

CHART No. 1: B. H. Showing favorable effects of parathyroid extract upon the weight, urinary volume and serum calcium.

to her home, but continued the parathyroid extract twice a week for a further period of three months. One and a half years after discharge she reported that she was still practically free from edema, but that the urine contained large amounts of albumin, Her blood pressure had not risen.

Comment: This patient presents a pure chronic nephrosis, with a normal basal rate. She reacted unfavourably to thyroid treatment, but gave very definite results following the use of parathyroid extract. Her edema was controlled, but there was no change in the albuminuria, or in the plasma protein values.

Case No. 2: Miss I. H., aged 4 years, admitted August 1925 to the Pediatrics Service of Dr. S. G. Ross. The child came from a charitable institution. It was stated that swelling had commenced suddenly three days before admission, beginning in the left ankle and spreading to the legs, abdomen, face and arms. There was marked frequency of urination, the volume was good, and the urine was free from blood. There was no history of previous illness or infection.

Physical Examination: Temperature and pulse were normal, but the respirations were somewhat increased. The legs, arms and face were extremely edematous, and the abdomen distended. Pallor was a marked feature. The throat was reddened, the tonsils buried. The lungs and heart were normal, the blood pressure 106/78. The liver edge could be felt 1 cm. below the costal margin. The urine was acid, cloudy, specific gravity 1036, albumen 15 grammes to the litre, and there were many granular casts and leucocytes.

The blood Wassermann was negative, and the fundi normal. The blood showed a well-marked nitrogen retention, the non-protein nitrogen being 65.4 mgms. per 100 c.c. The serum calcium was low (8.2 mgms. per 100 c.c.) while the cholesterol was increased to 438 mgms. per cent. The plasma proteins were depressed to 5.1 per cent, with an albumin globulin ratio of 1:2, the reverse of normal values. Owing to the patient's age and lack of co-operation the basal metabolic rate could not be determined.

Clinical Course: High protein with low fat diets had no effect on the edema, but on two occasions during her stay infections with high fever were followed by marked loss of edema. At the period when the serum calcium had fallen to 5.6 mgms. per cent, 50 units of parathyroid extract (Collip) were given hypodermically, each day for 11 days, with a rise in the calcium to 8.5 mgms. per cent; but without any marked diuretic response and with a stationary weight curve. At this point one of the bouts of fever commence and in 7 days the weight dropped 3 kilos. With the disappearance of the fever, the weight increased and two further courses of parathyroid medication failed to produce any effect either upon the calcium or the urinary output. The plasma proteins remained unchanged and the blood cholesterol remained at its high level (424 mgms. per cent).

Ten months after discharge the patient returned for observation. Her thyroid now was distinctly enlarged and the basal rate was 26.9 per cent

below normal. There was no edema and yet the cholesterol was 675 mgms. per cent, the plasma proteins were low, and the albumin globulin ratio was still reversed.

Comment: The second case is regarded as a glomerulonephritis with nephrosis on account of the urea retention and the occasional finding of red blood cells in the urine. Parathyroid extract had no effect, but in view of the subsequent enlargement of the thyroid and lowered basal metabolism, it is possible that had thyroid treatment been employed, her stay in hospital might have been curtailed. At the time of the first admission, however, nothing suggested a lowered thyroid activity. Another point is the absence of any apparent connection between the hypothyroidism, high blood cholesterol and low plasma proteins, and the presence or absence of oedema.

Case No. 3: R. F., aged 22 years. Admitted September 1926. He stated that albumin had been found in his urine in September 1925 at an insurance examination. In December of the same year he had a "grippy cold," but made a good recovery. In February 1926 swelling of the eyelids, ankles and legs was noticed for the first time, but he continued to work for another month. In spite of a diet without meat, eggs or salt, the edema gradually increased, and he spent the months of July and August in bed on a milk diet, again without benefit. Finally he was admitted to the hospital. There was no vomiting, his vision was good, there was no frequency or dysuria, but exertion produced dyspnea and palpitation. He gave no history of infection, except colds in the head, which were ascribed to chilling after strenuous exertion—he was an enthusiastic amateur boxer.

Physical Examination: Temperature and respirations were normal. There was moderate edema of the face and legs and the abdomen was prominent. The skin showed the characteristic alabaster pallor. The teeth, tonsils and sinuses were not infected. The lungs showed a few râles at the bases. The heart was not enlarged to percussion, the sounds were regular, well heard, and there were no murmurs. Blood pressure was 142/92. There was considerable ascites, but the liver was not enlarged. The urine was acid, specific gravity varied from 1012 to 1024, and the albumin averaged 6 grammes per litre. There were many granular casts and leucocytes in the sediment. For one week after admission red blood cells were found in the urine but were not present at later examinations.

The blood Wassermann was negative and the fundi were normal. The blood count was that of a secondary anemia with 3,950,000 red blood cells, 9,500 white blood cells and 70 per cent hemoglobin. The blood urea was 0.36 gramme per litre and the concentration factor (McLean) showed a moderate depression of kidney function. The Mosenthal test with a restricted variation in the specific gravity, a low night concentration and high night volume, confirmed the diagnosis of a beginning failure of kidney function. The serum calcium was 7.8 mgms. per cent, and the cholesteral increased. The total plasma proteins amounted to only 5.49 per cent with a characteristic albumin globulin ratio

of 1:2. The basal metabolic rate was not determined at this time.

Clinical Course: For the first two weeks after admission there was a rapid increase in the edema, in spite of a marked restriction in the fluid and salt intake. The low calcium values suggested that parathyroid extract might be of value, and a daily dose of 50 units was given for 5 days. The calcium rose to 10 mgms. per cent, but the rapid increase in weight continued. After 7 days he received a second series of injections, and in addition 6 grammes of calcium lactate were given daily by mouth. Although the serum calcium showed a well-marked rise, the urinary output actually fell to half its previous level (See Chart No. 2). The patient was now greatly distressed by the edema, the ascites was extreme, and many lineae atrophicae made their appearance about the hips and flanks. The abdomen was tapped and 3,500 c.c. of opalescent straw-coloured fluid of low specific gravity was withdrawn, giving considerable relief.

Two days later a high protein diet (P. 120; F 50; CHO. 250) was begun, and this was followed by a definite diuresis and loss of weight. With this diet there was a rapid rise in the blood urea, due in part to the rapid excretion of water, and the high protein feeding was discontinued. The diuresis ceased almost immediately; there was a steady gain in weight and in two weeks the maximum weight had been regained. At this point a second period of high protein feeding (P. 120; F. 70; CHO. 250) was begun but the weight remained unchanged.

Early in January 1927 (Chart No. 3) the basal metabolic rate was found to be -30 per cent, and owing to the failure of parathyroid extract and of the high protein diet, thyroid medication was commenced. Dessicated thyroid gland (B. W. & Co.) was used. This product contained 0.4 per cent organic iodine. At first 10 grains were given each day; this was followed by a daily dose of 20 grains for 11 days. Six days after the commencement of this treatment the urine volume gradually increased, the weight fell, and the basal rate rose; but when it had reached -16 per cent the further use of thyroid had to be discontinued because of marked nervousness and tachycardia. With the stoppage of thyroid medication the weight showed a gradual rise, the urinary output decreased, and the basal rate fell rapidly to 28 per cent below normal. With the resumption of thyroid gland at a more conservative level (10 grains daily for 1 week, 20 grains for a further week, then 10 grains and finally 5 grains) the diuresis began once more, the edema disappeared and the basal rate gradually rose to normal.

Cholesterol Values: During the latter part of this period the cholesterol showed a gradual fall with the rising basal rate, commencing at 600 mgms. it fell to 300 mgms. per 100 c.c.

High Protein Diet: While thyroid was being administered the patient received successively varying proportions of protein, fat and carbohydrate in his diet, but the diuresis persisted quite independently of the type of diet used.

Total Plasma Proteins: There was in this case the same lack of relation-

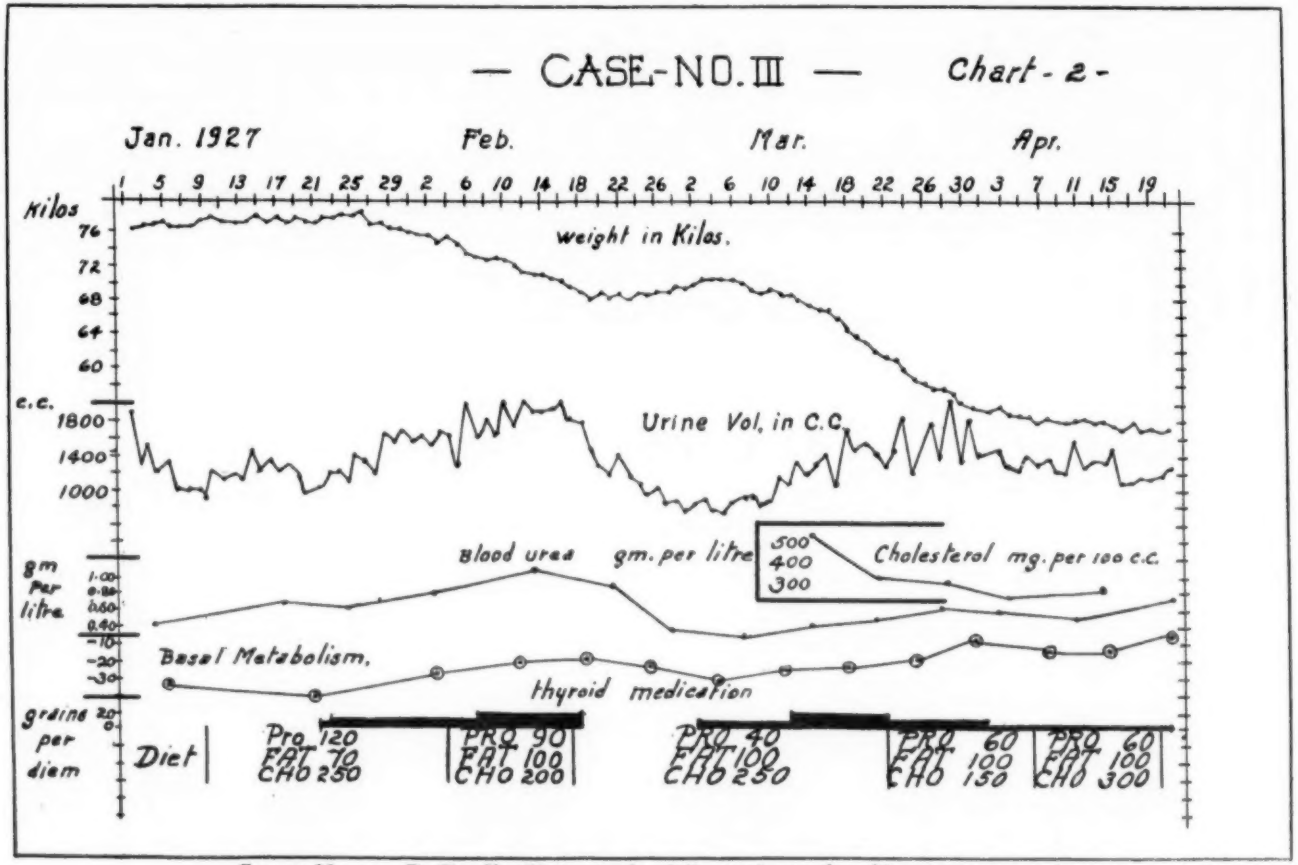

CHART No. 2: R. F. To illustrate the failure of parathyroid extract to produce a diuresis, in spite of a definite rise in serum calcium. Well marked diuresis and loss of weight during high protein diet, but with marked rise in blood urea.

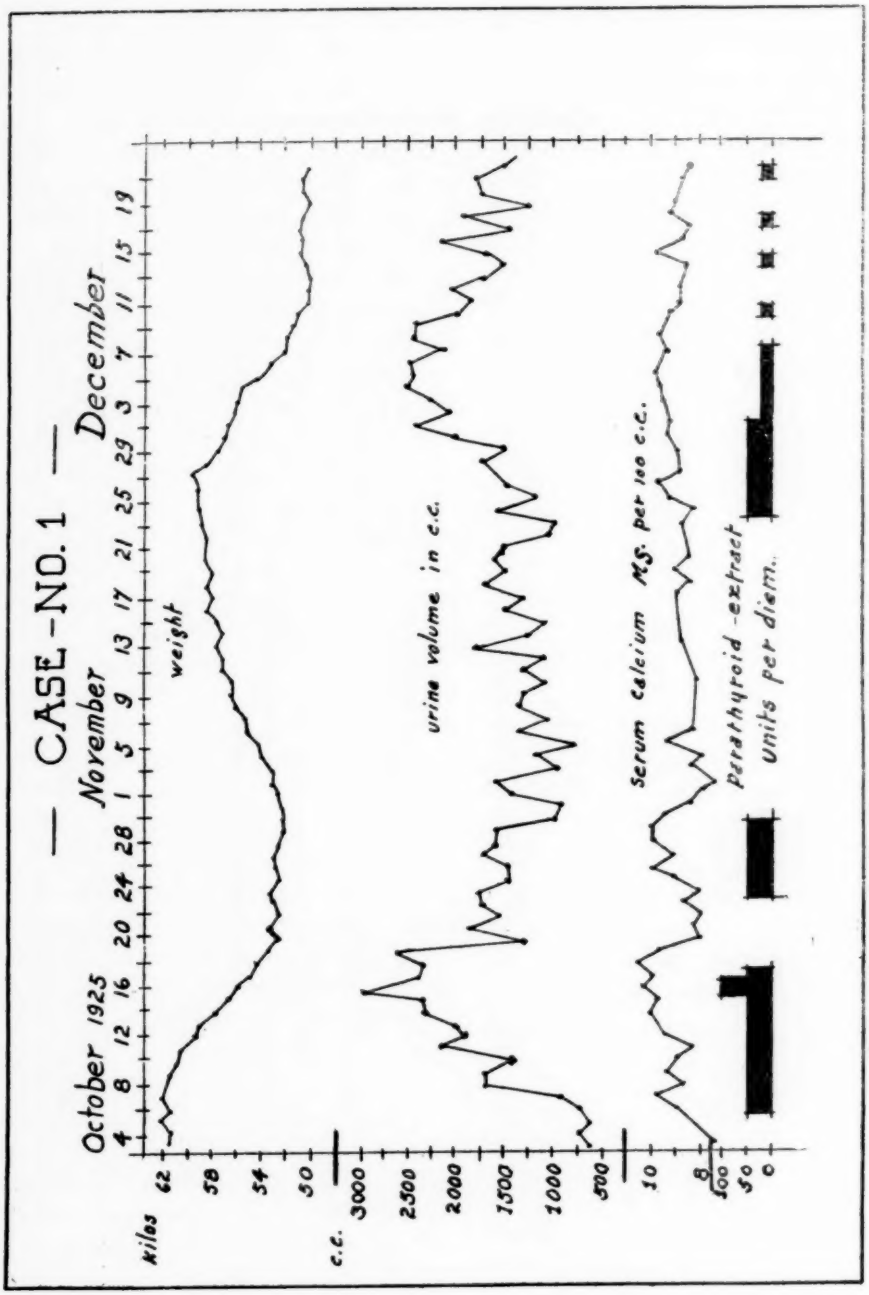

CHART No. 3: R. F. Failure of high protein diet to produce diuresis at a later date in same case as Chart No. 2. Favourable response to thyroid medication independently of diet—but with rising basal rate, increased urine volume, falling weight and blood cholesterol.

ship between the degree of edema and the concentration of the plasma proteins, as has been noted by others. During the period when 20 kilos of edema were excreted, the plasma proteins were always in the vicinity of 5.0 per cent and the albumin globulin ratio showed the typical reversal. These figures are given in the following Table:

TABLE 1
RELATION OF PLASMA PROTEINS TO EDEMA

Date	Total Plasma Proteins per cent	Albumin : Globulin ratio	Edema
1926			
Oct. 25	5.49	1 : 2.0	Increasing
Nov. 19	4.91	1 : 2.5	Decreasing
Dec. 1	5.04	1 : 2.5	Stationary
Dec. 10	5.11	1 : 2.1	do
1927			
Feb. 2	4.21	1 : 1.6	Decreasing rapidly
Mar. 13	4.46	1 : 2.3	do
Mar. 22	4.25	1 : 1.6	do

Calcium Metabolism: During the administration of thyroid gland, the calcium in the serum showed a gradual rise and eventually became normal. Reference to the succeeding Table will show the gradual rise which took place:

TABLE 2
RELATION OF SERUM CALCIUM TO THYROID FEEDING

Date	Serum Calcium mgm. per 100 c.c.	Dessicated Thyroid grains per diem Gland
1926		
Dec. 10	7.3	0
1927		
Feb. 2	8.5	10
Feb. 14	8.2	20
Mar. 11	9.2	10
Mar. 22	8.5	20
Mar. 28	10.2	10
Apl. 13	9.8	5
Apl. 21	10.3	5
May 2	10.0	5

Aub (16) has shown that in hyperthyroid states, calcium is mobilized from the bony reserves, and the gradual increase in serum calcium found in this case was probably due to the large doses of thyroid which this patient received.

Albuminuria: Epstein claims that the albuminuria tends to disappear following the use of thyroid treatment. The present case is an exception, the albumin not being reduced.

Eyegrounds: In October 1926 the fundi were normal, six weeks later definite blurring of the right disc appeared, with fine deposits of exudate; two weeks later the left eye also began to show definite changes. At first these changes were progressive, considerable exudate was deposited and there was a moderate number of small hemorrhages. With the clinical improvement there was a marked recession of the damage, so that in March 1928 nothing remained except a few scars at the site of the hemorrhages and a slight filling of the cup of the right nerve head. The vessels were normal and the vision 6/6 in both eyes.

Blood Pressure: The tension begin-

ning with a high normal reading (142/92) gradually rose to 180/95 and was still 160/100 fourteen months after the observations were begun.

Comment: The third patient is again an example of the mixed type, a chronic nephrosis grafted upon a glomerulonephritis. The increased blood pressure, the hematuria, the tendency to increased blood urea and the retinal changes all indicate the preesnce of an actual nephritis. The low basal rate, the hypercholesterolemia, the low plasma proteins, with the reversal of the albumin globulin ratio and finally the marked improvement of the edema following the use of massive thyroid dosage all point to the added presence of a true nephrosis. The patient is still free from edema and is at work, but requires 5 grains of dessicated thyroid gland daily to control the edema.

Case No. 4: H. G., aged 45 years, has been observed in private practice since December 1925. In 1920 he had an acute nephritis with marked edema which lasted almost a year. Following twelve months in Barbados, the edema disappeared with the exception of slight collections about the ankles. In 1922 he had a severe attack of scarlet fever with cervical adenitis. Since the initial nephritis his urine has been markedly albuminous and he has been very pale. Nocturnal frequency (two to four times) has been constant; there have been no other symptoms of kidney disease. His diet has been low in protein. Apart from typhoid fever in 1905 and recurrent nasal polyps, there have been no other illnesses and his weight has remained fairly constant since the disappearance of the massive edema in 1921.

Physical Examination: (January 1926). Temperature, pulse and respirations were normal. There were no evident foci of infection in the mouth. The nose showed many polypi in the left nostril. The lungs were clear, the heart was normal except for a soft systolic murmur at the apex. Blood pressure was 140/90. The abdomen was flat and the liver and spleen were not enlarged. The urine was acid, specific gravity 1023, and contained 13 to 15 grammes of albumin to the litre. There were many leucocytes, a few red blood cells, and also a few hyaline, granular and leucocytic casts.

The fundi were normal. The blood urea 0.55 gramme per litre. The Mosenthal test showed a variation of 9 points in the specific gravity, with a nocturnal polyuria and a low night specific gravity. The concentration factor (McLean) was depressed (16.0).

Clinical Course: During 1926 and the early part of 1927 there was no obvious change in his condition, except for a rise of 10 millimetres in both the systolic and diastolic pressures. In June 1927 his total plasma proteins were found to be low (5.8 per cent) and the albumin globulin ratio was 1:2.2. The blood cholesterol was 368 mgms. per cent, and the calcium 8.9 mgms. per cent. The basal metabolism was 16 per cent below normal. He was given dessicated thyroid gland in gradually increasing doses until he was taking 10 grains daily. In all he received about 300 grains in six weeks. There was no

change in the pulse rate, nor was there any other sign of hyperthyroidism, but the blood pressure rose to 190/110 and he stated that he did not feel as well as before. The albuminuria was unchanged. The thyroid was stopped on October 21st, 1927. Ten days later he complained of failing vision and both fundi showed small hemorrhages. His sight gradually improved, but the edema and dyspnea became more marked. On January 30th, 1928, he suddenly noticed marked loss of vision, and on examination a marked hemorrhagic neuro-retinitis was found in both eyes. The blood pressure was now 220/130 and nocturnal dyspnea was a troublesome factor. Vomiting, headache and other uremic symptoms appeared, and on March 21st he had a severe convulsion followed by a pronounced toxic psychosis, and from that time the patient has presented all the signs of a slowly progressing uremia.

Comment: The fourth patient shows a mixed glomerulonephritis and nephrosis. He is presented chiefly as an instance of the unfavorable effects of thyroid medication. There is no doubt that the disease was a progressive one, but its advance seemed to be definitely hastened by the endocrine treatment.

Conclusions

That lipoid or chronic nephrosis is a definite clinical entity scarcely can be doubted, but by many it is regarded as a clinical curiosity and of infrequent occurrence. This is true of cases of pure nephrosis, but the mixed types can be recognized more frequently if careful studies are made of the so-called parenchymatous nephritides with oedema. Pure lipoid nephrosis is seen most commonly in youth or early adult life, and while this is also the case with the mixed types, they are also seen in those of more advanced years, (Case 4). There have been seven fully identified cases of the mixed type in this clinic within the past two years.

While extended chemical studies are necessary for the absolute recognition of nephrosis, its presence should be suspected where there is the history of an insidious onset, a long continuing edema, a copious albuminuria, and marked pallor, without evidence of cardio-renal involvement or hematuria. The presence of a milky plasma in these cases, noted a century ago by Bright, is an added diagnostic feature.

Endocrine Origin:

In five of the seven cases referred to, there has been thyroid insufficiency. Of the four cases reported, two showed rates varying from 16 to 30 per cent below the normal, while a third (Case 2) showed a rate 27 per cent below normal one year after her initial studies. The marked tolerance to thyroid medication shown by these patients has been stressed by Epstein (8), Murphy and Warfield (4), and others. Large doses of thyroid are required to produce effects on the basal rate. Case 3 shows this tolerance to a moderate degree. A daily dose of 20 grains of dessicated thyroid gland was required to produce a noticeable rise in the metabolic rate, but the normal rate, once established, was maintained by a daily dose of 5 grains.

It should be borne in mind that thy-

roid medication is not without its dangers. Such a possibility has been suggested by Bower and Boothby (17) in nephritis with normal basal metabolism, but in our case (No. 4) even with a rate 16 per cent below normal, the results were unfortunate. There were no signs of thyroid over-dosage, but his clinical condition became so much worse after thyroid medication that it seemed more a result of the treatment than a mere coincidence.

The first case is of interest in that parathyroid extract gave a remarkable response after thyroid had been used without success. The parathyroid extract was given because of Davidson's (13) report, and because of the low serum calcium values. The mode of action of parathyroid in nephrosis is uncertain. Collip suggests a depletion of the body fluids due to the hypercalcemia, but in the third case satisfactory rises in calcium were obtained with parathyroid extract, but without any diuresis. Further investigations of the changes in distribution of the ionized ond non-ionized calcium may clear up the difference between the response of certain cases to parathyroid and the lack of response in others.

Calcium Metabolism:

Extensive studies of the calcium metabolism have been made in the second and third cases of this series, and are to be published separately (W. de M. S.). Beyond the generally low serum calcium found in nephrosis, the chief clinical interest is that the third case, with a lowered calcium, showed a gradual rise of the calcium to normal values under thyroid medication. Similar findings have been reported by Aub and Bauer (16) in cases of hyperthyroidism and have been ascribed to a mobilization of calcium from the bones, which show definite X-ray changes after prolonged periods of thyroid over-action.

Hypercholesterolemia:

In the second, third and fourth cases there were definite increases in the blood cholesterol. The third case showed remarkably well the relationship between the cholesterol and basal metabolism. An association of increased cholesterol and arterial changes has been noted in diabetes, but in our third case X-rays failed to show any calcification of the peripheral vessels even after a prolonged period of hypercholesterolemia.

Albuminuria:

Epstein (3) (8), Davidson (13) and others report that the albuminuria tends to disappear following the use of thyroid preparations. This refers more particularly to the pure chronic nephrosis. Our cases treated with thyroid were of the mixed type, and have not shown any decrease in the albuminuria, although two have now been followed for two years and two for shorter periods. It is of interest that all of these individuals with persistent loss of albumin, continue to show the low plasma proteins and the reversed albumin globulin ratio, although three of them are quite free from massive edema.

Prognosis:

The cases under review do not offer any new information regarding the outlook in this type of disease. The picture seems to be that of a chronic

lesion from which few fully recover and these are of the rare, *pure* nephrosis type. A considerable number show marked improvement and are capable of much useful work, while others show a gradual progress of the associated nephritis. The prognosis is complicated by a marked lowering of resistance to infections, and there is a considerable mortality from this cause.

Summary

Four cases of chronic nephrosis are presented. The first is a pure chronic or lipoid nephrosis, the other three are examples of chronic nephrosis with glomerulonephritis. These patients have been treated with parathyroid and thyroid preparations. The first case showed a marked response to parathyroid extract, the second and third showed no response. The second patient became edema-free after all treatment had been discontinued. The third case became free of edema following the use of massive doses of dessicated thyroid gland. The fourth showed a rapid advance of the disease following thyroid medication. In no instance was the albuminuria affected by treatment, nor did the plasma proteins or albumin globulin ratio show any noticeable change, even when marked symptomatic improvement occurred.

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The Treatment of Rheumatism*

By Harlow Brooks, *New York City.*

ANY paper on the subject of "Rheumatism" at this time might almost be properly begun with an apology, for the reason that all clinicians of today are much confused in their own minds as to just what is meant by rheumatism. To many, rheumatism still means any sort of arthritis or almost any disease condition which is largely characterized by a nontraumatic joint inflammation. Others of us demand as a requisite that the term "rheumatism" be limited to a disease process in which an arthritis appears as an evidence of a generalized infection. This would then also include those not infrequent instances of arthritis caused, for example, by the pneumococcus or the staphylococcus, by the gonococcus or perhaps even those very interesting cases which are caused by syphilis, either acting alone, or in combination with other infectious factors. It is quite certain also that those rare cases of arthritis arising in influenza must be also considered in this relation. Most, if not all, of these instances are, it is true, differentiated often with great difficulty from cases of true rheumatism, and there can be little doubt but that many instances of true rheumatism are thus complicated by these additional infectious agents. That this is a very frequent occurrence is obvious to any clinician of wide experience.

Since the early work of Poynton and Payne with their diplococcus in particular, however, the observant clinical worker has become more and more convinced that a coccus, or a special streptococcus is the essential etiologic factor. Recognition thus far of a special and specific streptococcus has not, however, as yet received the full acceptance of clinicians. Even those such as Pemberton, Small and others who have done very much to establish a specific streptococcus as the causative factor in rheumatism, cite without exception special strains of the organism which characterizes the disease. That it is highly probable that these strains may merge more or less one into another and that biological modifications and transformations take place until a more or less generalized group of streptococci is reached, seems from the clinician's viewpoint a strong probability.

It is small wonder then that the clinician finds great difficulty in recognizing in his own mind any definite clinical picture dependent on a specific pathogenesis which permits him to unqualifiedly identify the highly polymorphic clinical instances of the dis-

*Read in abstract before the Association of American Physicians, May 3rd, 1928.

ease as a definite entity. This attempt at sharp classification is, therefore, as yet not successful even when every facility necessary for full bacterial study exists. Where a strict bacterial classification is insisted upon there exist also numberless instances of even definitely certain clinical types of typical rheumatic fever which must on bacterial grounds be excluded from the group.

But the clinician must continue to study and treat these cases. The matter is, however, much less difficult and less confusing as we go on from year to year, and now in acute instances the recognition is no longer so very difficult, but in the subacute and chronic cases, in point of frequency of occurrence the difficulty of treatment increases tremendously. The difficulty of attaining a satisfactory therapeutic result augments as chronicity increases.

To a larger extent in the greater institutions and in the larger cities, these cases fall to a considerable and growing number to the care of the specialist in arthritic diseases, but the average internist and notably the general practitioner is still called upon to bear the brunt of therapeutic management either because of lack of specially skilled talent or because complications of the circulatory, renal or other systems require the service of the broadly, rather than that of the narrowly trained man.

This paper has been prepared from the standpoint of this general internist. My experience has been derived from a service of over twenty years in the general medical wards at the City Hospital and from that of an even larger number of years as a medical consultant to the Hospital for Joint Diseases, where my association with highly trained specialists and a highly specialized service has given me, I hope, a very broad viewpoint on this difficult but fascinating subject.

So very much recent and highly elaborated literature is now available in the medical press that I shall not enter into the minutia of specific treatment to any intimate degree though I shall presume to criticize, perhaps unwarrantedly, from the broader viewpoint of the internist whose views of the abstruse problem should be at least valuable from the standpoint of the patients as a whole, even if not as an exposition for the demonstration of minute problems in the study of arthritis as a speciality.

There is, I find, a very certain danger that in our more minute classification of the arthrites and of the newer methods of treatment that we may lose sight of those general methods of management which past experience has shown to be of very definite and imperative value in the treatment of cases. Inevitably it must happen then that much that I shall say will be but recapitulation of methods long familiar to most of you, but I can assure you that my contacts with the newer methods of treatment have shown me that very many practitioners need not be now reminded that the new in the treatment of arthritis of rheumatic origin is not therefore necessarily the most productive of good results nor of the most ultimate benefit to the patient. I hasten to state, however, that my contacts with those specialists of greatest experience in the

use of the newer methods have convinced me that in so far as their individual practice is concerned they have apparently in no way lost their confidence or facility in the employment of the old and more or less standardized methods and drugs.

For the purpose of convenience in discussion it is advisable to consider the subject under the headings of Acute, Subacute, Chronic or Mixed cases. Everyone of course understands, however, that the one merges imperceptibly into the other, and also that at any time in a subacute or chronic case acute exacerbations may appear, sometimes without any premonitory warning, and very often, without any apparent exciting cause.

Both from the standpoint of the general disease process as well as from that of the joints the most primitively important essential in treatment is rest. Traumatization of a joint in the course of rheumatic fever will almost certainly determine a localization of the disease in that area. It is very possible then that the same may take place as regards the internal viscera. That is, for example, that overaction of the heart may predispose that organ to rheumatic invasion. Certain it is that cases which are promptly put at rest ordinarily do better, and as a rule present fewer complications than those which are allowed to be up and about. Abortive termination of rheumatic fever apparently occasionally occurs when thorough rest is enforced. Another closely involved factor may appear in this relation for if exposure to chill, to wet and the like takes place in the course of the disease apparently the process is definitely activated so that with the enforced rest must be correlated protection from chill and exposure. The old recommendation that the bed clothing and even that the garments of the patient be constructed of wool or of some similar non-conductive and absorptive medium has been found very beneficial both as regards the comfort of the patient, and also because it may in some perhaps indirect manner thus modify the severity or spread of the disease in the tissues.

The bed itself is an extremely important matter. It must be of proper height, narrow enough to permit of easy handling and dressing of the patient; hard enough so that depressions and ridges will not form to annoy the patient, and springy enough so that its hardness will not be rigidity. Much comfort is added for the patient by the arrangements of hoops, trestles, or other devices to keep the pressure of the bed covers from hurting the diseased joints. Sand bags, pillows and pads made of suitable material may be used to fix the involved extremity so that constant shift of position does not bring about pain.

Fixation of the joints affected is a direct indication from the symptoms of the patient because joint movement is inevitably made at the expense of considerable pain. Immobilization of the involved joints can be most satisfactorily carried out in most instances at least by the use of light splints constructed of paper board or similar material. It is probable that some of the benefits attributed to the action of drug impregnated dressings may be the result of the joint immobilization, at least to some degree, but there is

also no question of the benefit, at least in immediate comfort to the patient which follows from the application of warmth to the joint by wrapping it in absorbent cotton or soft woolen loose dressings with at times the local application of heat by the electric pad, hot water bag or when neither is available, by heated sand bags or bricks. There are cases which appear to derive more comfort and rest from the use of cold applications, but these are in my experience exceptional. I have found it the rule that wet applications are in general to be avoided and this is in my opinion one of the arguments against the use of many of the wet applications, such as lead and opium wash and the like. As in most things, there are exceptions. I have obtained marked relief of local pain from the wrapping of the joint in dressings saturated with concentrated solutions of magnesium sulphate, aluminum sulphate, and other desiccating preparations.

Mostly the older clinicians are still somewhat in favor of the use of various oleaginous preparations often containing medicaments, such as petrolatum with oil of wintergreen or other drugs supposed to have an anesthetic effect on the pain. My own experience has not inclined me to look on this method with favor, nor have I seen commensurate proofs that these preparations act in this regard. Ichthyol and other similar drugs have been thus used with in some instances the expectation that some specific benefit might follow. They have been useless in my hands.

Counter irritants, such vesicants as menthol, thymol and the like have been used, oil of mustard and so on, but in my opinion without benefit and at times ugly vesication with subsequent local ulcerations have taken place. Similarly I have not seen benefit follow the local use of electricity in the treatment of the acute joints. Possibly I may be too pessimistic in this regard, but it is also possible that my definite inclination to interfere as little as possible with the patient in this disease may have unduly prejudiced me.

In regard to this last point, however, I do wish to point out my entire belief that the patient should receive a general inspection or examination at least once daily. This can be encompassed, generally, without much annoyance to the patient. The sinuses of the skull should receive frequent inspection for an infected sinus may indeed be the probable portal of entry of the infection. The state of the throat especially as regards possible tonsillar abscess, ulcerations and the like should always be considered, for if any of these conditions exist or develop in the course of the case, no real conclusive benefit in treatment can be expected, unless the suppurative focus be evacuated, though it must never be forgotten that in this disease the opening of new blood vessels and lymphatics to infection must be avoided if possible, and in my experience the removal of the tonsils in the active phases of the disease is always a hazardous procedure —obviously this does not pertain to the drainage of an abscess or that of an infected sinus, which may at any time become an imperative requisite.

Believing as we now do that, in many

instances at least, rheumatism originates from occult or hidden foci of infection, particularly such as do not drain, and that the portal of entry is in many instances of this nature, it would seem to be an obvious procedure, but experience has shown most of us, particularly those of us who have had an extensive experience, that radical procedures during the height of an infection are frequently attended with a dissemination of the infection. Sometimes indeed a generalization of the infection may take place under such interference with the involvement of new joints, the appearance of endocarditis, pericarditis, acute glomerular nephritis, and so on. This fact pertains particularly as regards radical dental procedures. While I feel that the extraction of definitely infected teeth during the course of an attack of rheumatic fever in which the primary focus by exclusion may be attributed to a dental infection may at times become imperative, I wish to particularly caution against the unsurgical use of the curett which is so frequently now employed by dentists after extraction in these instances. Incidentally, also I wish at this point to voice my frank disapproval of widespread dental extractions on very flimsy evidence which are now in such frequent vogue in this and other infections. It is probable that dental infections play but a very subordinate rôle in the etiology of most cases of rheumatism. The relationship between tonsillar infection and rheumatic fever is a much more definitely proven matter. While I have pointed out above that the relief of tonsillar abscess in the course of the disease may be imperative, radical tonsillectomy is to be then definitely advised against because of the frequency with which endocarditis, myocarditis, septicemia, embolic phenomena and usually marked exacerbation of the arthritis take place under such circumstances. Pulmonary embolism and abscess formation are frequent in such cases.

Our recognition of rheumatic fever as a definite infection and at this stage as in nowise a metabolic disturbance has greatly modified and improved our dietetic management of the disease. In general the diet should be that employed in any other acute febrile disease, but because of the striking tendency in this disease to develop severe grades of anemia which serve to greatly depress general resistance and to much prolong convalescence we now attempt as much as possible to give iron-rich foods, the meats, bone marrow, liver, the green vegetables, egg yolks and the like, whenever the temperature and general condition of the patient's digestion permits. The severe grades of anemia which have in the past been so characteristic of this disease should not be permitted to develop and throughout the course of the disease the various iron preparations may be given, including, when necessary, fractional or even massive blood transfusions.

Excretion is to be favored throughout by the copious administration of water in one form or another, as for example, in the fruit juices. There are large losses of body fluid from the severe sweats which are prevalent in the disease and there is a belief that the renal well being is to some extent favored by the administration of water

in large amounts. There is no doubt in the mind and from the experience of the author that the alkaline waters are of definitely beneficial effect in this disease. There is excellent ground in modern practice substantiating the value of the old so-called alkaline line of treatment in this disease and this can not be more advantageously given than in the form of the alkaline waters.

It goes without saying that the bowels should be kept freely open in rheumatism, and here again this can be usually well effected by the use of water in abundance, especially by the alkaline waters, and when need be by the further addition of such alkaline saline laxatives as may be required.

In such a disease as this in which the sweating is so marked it is clear that much comfort may be also afforded the patient by careful attention to the skin. Frequent sponge baths, carefully and gently administered, add greatly to the patient's comfort and sense of well being. Except when it is advisable to attempt to reduce excessive temperature by the use of cold or cool water, warm water sponges are by far the most advisable. It is problematic indeed how much is to be accomplished by hydrotherapy in this disease beyond the good wrought by the alkaline waters internally and by the use of water externally in ordinary bathing.

A tremendous amount of discussion has been wasted on the question as to the value of the salicylates in rheumatism. This discussion has rarely developed among experienced clinicians it is true, and the chief point of argument that has been brought against their employment has been due to the simple fact that we are as yet entirely unable to explain how they may affect the infection. That they tremendously allay the suffering of the patient, that they add to his comfort probably more than all our other therapeutic factors put together is a clinical axiom. It is nonetheless perfectly true that we cannot as yet any more definitely show how they work this end or how they affect the actual disease producing factors, whatever they may be, than we were a few years back able to explain the equally disputed effect of mercury in syphilis or to scientifically explain the action of quinine in malaria before the discovery and identification of the specific organism which is its cause. The salicylates are equally beneficial to the patient with rheumatism in so far as his comfort is concerned at least. Much, very much, is to be learned by all of us as to the use of the salicylates. No one routine form or manner of administration of the drug will suffice. Individualism is perhaps nowhere more obviously demanded than in the use of the salicylates in rheumatism. There is no one form of the drug which is universally most beneficial and there is no one manner of administration which will suffice to give the best effect in each individual case. Unless the clinician is prepared to accept this fact, and to profit his patient by his acceptance, he is doubtless quite entitled to pessimism as to the value of this large and rapidly augmenting class of drugs in this disease. "Ward treatment" will never succeed with the use of the salicylates in this disease, at least not in comparable degree with the skilled and

individualistic use of the drug in patients with this infection.

Very many patients are extremely intolerant to certain of the forms of the salicylates. Perhaps there is no other drug to which intolerance is more definitely and individually shown. Many patients can tolerate only certain forms in full therapeutic doses. Still others are unable to take it in sufficient doses through but a single manner of administration. This pertains in particular to the usual method of administration by mouth. There are, however, few patients indeed who are unable to take at least some form of the drug and there are many effective forms of the drug on the market, and the skilled clinician who wishes to do full justice to his patient should try to familiarize himself with many or most of these if he wishes to get the maximum benefit from the salicylates.

Another matter of elemental importance is the recognition of the fact that most patients develop an intolerance for any specific form of the drug after it has been taken for a few days, or, which is equally important, the disease seems to develop a tolerance for the special form of the drug so that it soon ceases to give the desired benefit. Frequent change of the form of the drug gives in nearly all instances the maximum best effect with the smallest degree of uncomfortable symptoms from the drug itself. Frequent change of form and also of manner of administration enables the use of maximum effective dosage. The failure of some clinicians to adequately appreciate the possibilities of the drug is due in considerable part to their failure to recognize these essential facts.

There is also a very great difference in the potency and toleration qualities of special salts of the drug as they are produced by various manufacturing chemists. Some of the synthetically prepared drugs are much more difficult to tolerate than the natural forms of salicylic acid as derived from crude sources. Degrees of solubility also differ widely. For those of you who find it difficult to rationalize these facts it may perhaps suffice to compare the salicylates and their toleration to that of certain food substances in their reactions; this is most strikingly evident when compared with national habits of food selection. The required dosage is also largely a question of individualism. This must be measured not in centigrammes but in therapeutic effect. It will be found to vary tremendously. As a rule most physicians use the salicylates in too small rather than in too large doses, but large dosage in many cases is entirely unnecessary. The symptom which is chiefly to be considered in dose determination is naturally that of pain. The proper dose in any case is the largest one which gives a striking relief of pain without the production of disagreeable drug symptoms.

Through the courtesy of a well-known drug house, I have recently been experimenting with the use of various salicylates combined with magnesia which seems to act with the salicylates much as magnesia does with morphia by intensifying its effect and making smaller dosage adequate, and at the same time reducing intolerance. J. E. Winter and H. G. Barbour, of

the Department of Physiology and Pharmacology of the School of Medicine of the University of Louisville, report in a recent number of the "Transactions of the Society of Experimental Medicine and Biology" a series of experiments concerning the use of magnesium chloride in association with the salicylates which has a probable direct bearing on this same problem. Their conclusions are as follows:

"I. Magnesium salts in mice appear to reduce the toxicity of salicylates (protective antagonism).

II. Magnesium augments the antipyretic action of sodium salicylate and aspirin. When given subcutaneously with salicylates to fevered rabbits, the earlier stages of antipyresis are characterized by marked synergism."

It is very probable that the relief of pain and of fever, if present, are very closely associated, and it seems also probable that some such similar action may explain the apparent greater therapeutic effect of the salicylates when given in association with magnesium in cases of rheumatism.

I have stated that the avenue of administration is advantageously modified to suit the individual patient. Obviously the most convenient thing is to give the drug by mouth. Generally it is better tolerated when given with food and commonly when given in solution rather than in any powder or as a capsule. There are many exceptions, however. Where therapeutic efficiency is accompanied by disagreeable drug symptoms, other drugs designed to correct these may be introduced, either with and through the same avenue or separately. The tinnitus, for example, is commonly well controlled by the bromides, by chloral, or by luminal, while gastro-intestinal irritation is mitigated or eliminated by sodium bicarbonate, salts of magnesia and the like, but in a few cases I have achieved my best result only by the combined use of very minute doses of cocaine, or atropine.

Rectal administration acts very satisfactorily for most forms of the drug, particularly for those which are water soluble. As a rule these drugs are given in solution or in suspension in about two to six ounces of water which has been slightly thickened by starch which renders the mixture much less irritating to the rectum. Much better toleration is effected when the rectal dose is introduced six to eight inches up into the rectum, practically into the sigmoid. Where one dose daily is given it is preferably given at night, and if so desired some sedative may be used with it. As a rule very large doses may be given in this manner without any irritative symptoms. 160 to 200 grains of the salt of sodium may be thus well borne for a considerable length of time before any signs of irritation or intolerance arise. The effect produced by rectal dosage is slower in action than when the drug is given by mouth, but the effect is prolonged very much over that attained by mouth administration. In some instances the drug may be given in suppositories. Acid acetyl salicylate is often very effective in this way. Usually I have my suppositories made up in cocoa butter, which is very well tolerated by the rectum.

Intravenous medication is chosen in many instances, particularly by those physicians who are fond of giving

drugs in this manner. It is particularly adaptable to the intravenous use of sodium salicylate. The drug acts very promptly when given in this manner and it will in suitable cases give quite as quick relief from pain as though morphine were given. The effects, however, pass away correspondingly quickly and the method is subject to the same occasional accidents which may appear with any form of drug given in this way. I am not accustomed to use this manner of treatment except when the pain is very severe and such as to merit very prompt relief. It may be used from time to time in association with the other methods of administration.

As a general rule I change the form of the drug every seven to ten days, so that less intolerance and fewer drug symptoms appear. It is also satisfactory practice to allow one form to be given until it appears to be losing its effect, or to produce disagreeable symptoms when the shift in type is to be considered. If, after a few days, the newer preparation of the drug is found less effective, of course another salt is used or a return is made to the first one.

As is the practice with most physicians, sodium salicylate is the form which is most commonly used introductorily by me. Where it is to be given by mouth I often specify that the natural drug be dispensed in place of synthetic products or that certain makes, perhaps more carefully prepared than others be dispensed, but when the administration is to be by rectum as a rule the ordinary synthetic preparations are used, of course in considerably larger total dosage than when given by mouth. With bed patients as a rule rectal doses are given two or three times daily, but ambulatory patients get but a single dose on retiring.

Occasionally acid salicylic is prescribed in association with sufficient alkali to produce a stable salt in the stomach or intestine. Acid acetyl salicylic is another very useful form of the drug. It is usually very well tolerated. The preparations manufactured by the standard chemists are reliable and contrary to the impression prevalent in some places, the drug is very safe, even in cases of serious heart crippling. In any case when uncomfortable rashes appear after the salicylates, epinephrine will give prompt relief as a rule. Salol is another very excellent form of the drug, but it should not be given when crippling of the kidney is suspected because of the liberation of its carbolic acid radicle after ingestion. There are numerous other effective preparations on the market. It is really curious how well they may be borne in certain persons when the more usual forms are not well tolerated, and how very effective therapeutically most of them are. Naturally it will be found that the less advertised preparations are usually the more effective, but it is well worth the while for any physician to attempt to familiarize himself with as many different forms of the drug as possible, if he is called upon to treat many cases of this disease.

Not only is toleration effected by the form of the drug but the menstruum in which it is given is also of importance. The art of prescription writing is fast becoming obsolete in

this country, in Germany and France, but suitable formulae may be found in many older text books. We are particularly prone to forget the possibilities of drug combination and of the utility of proper preparations in our hospital practice. Care in this respect is, however, notably required in private practice, and few physicians would dare to exhibit the same indifference and carelessness in their private work that they habitually do in their hospitals, where as a rule the whole of this responsibility is thrown on the hospital pharmacist, who prepares more or less carefully certain standardized mixtures. Not infrequently one can determine the probable size and character of a physician's practice by the care which he takes in the writing of his prescriptions.

There is great question as to the manner of effect of the salicylates in rheumatism. No doubt its most striking result is the reduction or elimination of pain. That it limits, prevents or repairs actual tissue change, to my knowledge, has never been definitely shown, but it is quite certain that under its effects the most striking lesion of the disease, that is the arthritis, subsides, at least in severity. It is alleged by some that its effect is purely that of an analgesic—it certainly is the best analgesic that we possess for the disease, but I think that there are few experienced clinicians who have not seen under its use apparent subsidence of the arthritis. Furthermore, most of us believe that it may definitely abort or prevent the disease in at least some of its instances, though manifestly this is a very difficult matter to prove. Not infrequently there is a definite reduction of temperature and an associated fall in pulse rate under the action of the drug. In some instances under my observation there has been a disappearance of cardiac arrythmia in instances of presumed rheumatic myocarditis with a reappearance when the drug was discontinued. It is very exceptionable that one sees, if ever, disappearance of the characteristic rheumatic nodules under the salicylates, or for that matter under any other form of treatment, unless it be under the effects of the iodides.

It must be admitted that the drug relieves more than it cures. It suffices, however, to make the disease tolerable in most instances and few patients who have once secured its relief will allow themselves to be treated subsequently without the drug. Physicians who are themselves subjects of rheumatism in chronic or subacute types in particular appear to be especially prone to the use of the drug.

It is in my mind very questionable if the drug prevents the development of complications, notably those of the heart. I do believe, however, that it does favor their benefit and cure, but it is impossible to ascertain to just what degree it is actually curative, especially when we are so very uncertain as to the real nature of the disease itself.

One can at least affirm that it is at least as curative as any other specific measure thus far available to us. I know of no clinician who fails to use the drug in his practice except when it is eliminated temporarily for experimental reasons, nor should I like to entrust any patient to the treatment

of a physician who fails to use this drug. My hospital and private practice observation has fully convinced me that it is only those who fail to properly comprehend the use of the drug who do not use it with definite benefit.

It is highly probable that the so-called alkaline treatment of rheumatism is only beneficial because it acts in a general way, that it has any specific action is very improbable, but it is nonetheless a very important adjuvant.

The iodides in my experience have little if any favorable effect in acute rheumatism. Later on I shall give reasons for their employment in chronic cases, or in those numerous instances in which mixed arthritis is present or where the disease is complicated as it frequently is, with certain metabolic disorders.

Treatment with foreign proteins in cases of acute rheumatism has met with some apparent success in my hands. My chief studies in this respect have been with sterilized milk and with various vaccines, some of autogenous derivation as from infected tonsils, infected teeth or sinuses and in some instances with the so-called stock vaccines procured both from experimental laboratories and also from standard manufacturers of the biological preparations. My most striking benefit has undoubtedly been derived from the intravenous use of minute doses of typhoid vaccine in acute cases. I have admittedly not pursued these studies sufficiently far to permit my opinion to be of any very great value in so far as my personal experience is concerned. I have never received from any of these methods relief comparable to that furnished, for example, by the salicylates, though in all instances the same general measures have been employed as with the salicylates. I have had very severe reactions in some cases especially from the intravenous use of typhoid vaccine. I am convinced that none of these measures are curative to any definite degree, at least in acute cases, and that none of them influence the occurrence of complications or mitigate their progress to any observable degree.

I have also observed in my own services and in those of my colleagues studies made with the various sera and vaccines now being employed so extensively all over the country. Some of these studies have been under the charge of my immediate assistants and associates and conducted on my own service. I have seen nothing as yet to convince me that anything of startling or substantial value has been attained in the specific treatment of acute arthritis of rheumatic origin.

The SUBACUTE types of arthritis which we ordinarily classify as rheumatic furnish a quite different aspect from a therapeutic standpoint. Here also the salicylates are extremely useful, particularly as to the relief of pain, though the salicylates are by no means so definitely startling in their effectiveness in the subacute form of the disease. Here more or less real deformity of the articular and periarticular tissues has taken place, fibrosis of greater or lesser degree has followed and in all probability important metabolic alterations have taken place together with muscle atrophy and defi-

nite trophic change in all the structures, including the nerve trunks and nerve endings.

Although the salicylates materially lessen pain and make joint manipulation possible and active and passive movements endurable, they do not apparently influence materially repair of tissue. They do, however, in my opinion prevent or abort acute exacerbations to a very considerable degree and they are necessary for the proper management of some cases. I do not believe that they facilitate resorption of the rheumatic nodules.

Various foreign proteins seem to me to be often very effective in these cases, though they may also excite exacerbation of old processes and cause considerable increase in suffering at times. I have used in these cases autogenous and stock vaccines, so-called specific vaccines and other proteins as sterile milk and occasionally horse serum and egg albumin injections with some benefit apparently not only in checking progress, but also in clearing away lesions of an exudative nature which had been already laid down. I have seen nothing to persuade me that I was dealing with anything more than a foreign protein reaction in any of these instances. I have not either used or seen used the method of treatment based on the work of Dr. Small, nor have I seen fairly represented protracted treatments along the lines advanced by several other well recognized investigators.

There is no doubt in my mind but that real benefit is furnished from this method of treatment in general provided that it is carried out in conjunction with other and older methods which have long been in use in such cases. I refer particularly to skillfully conducted hydrotherapy, to active and passive movements and exercises, proper attention to excretion, to muscle training, to the correction of anemia and malnutrition, maintenance of excretion and the like.

The diagnosis in CHRONIC RHEUMATISM is an exceedingly difficult and unsatisfactory matter. Most cases which are collected under this heading probably represent associated disorders and tissue changes which may be only remotely and secondarily related to the specific disease of acute rheumatism. In many cases complications with metabolic faults have taken place, urates and other salts have been deposited about the joints. Occasionally these cases respond very satisfactorily to treatment with colchicum, to the iodides and to dietetic restrictions or modifications. My experience has led me to feel that careful dietetic study is well worth while, in most of these cases at least, and a careful study of the blood and urine chemistry is essential. Only this and all the additional information that a very intimate clinical study of the case as an individual one can serve as an adequate basis on which to found an intelligent line of treatment.

Every possible source of residual infection should if possible be cleared away, the tonsils, the sinuses, the teeth, the gall bladder and the entire gastrointestinal tract must be considered as possible sources, and one must never forget the potentialities existing in the genital tracts, the cervix uteri, the prostate, seminal vesicles and in the urethra and vagina. The salicylates

may be useful to combat the pain if it is present, but they will now be found to be of minor effect even for this purpose. Excretion must be maintained at its maximum; water still remains as a most desirable medicament and the alkalies are of undisputed value. In this phase of the disease which can certainly no longer be considered as a specific, infection must be considered as an end result of many complicating sequences.

The treatment of the joints may be now the least important of our problem because of the almost certain serious involvement of the more important internal viscera, the heart and vascular system in general, the kidney, liver and especially the peripheral nerves which have become more or less seriously involved as a part of the atrophic processes which have developed in and about the joints and in the muscles and tendons in particular.

The management of the joint deformities and lesions of both an inflammatory and degenerative character must receive most careful study and consideration if even a minimum good effect is to be effected. Passive and active exercise of the joints must be practiced, massage, electrical treatments, most of all persistence must be insisted upon.

Holding well in mind the condition of the internal viscera and always considering their elementally important rôle in the case, efforts of a most persistent character must be introduced to clear away the joint lesions.

The iodides are of very great value in many of these cases. We need not speculate on the hopeless problem of attempting to reason out the action of the drug for we are now dealing with a very complex disease of the joints and surrounding tissues. Many cases are entirely unaffected by the iodides, some cases are distinctly made worse, but it will soon become apparent to the observant physician whether or not the drug is of value, and it may accordingly be pushed, continued merely, or entirely eliminated.

The use of vaccines, autogenous, if definite foci of inflammation are available for cultures, is attended in very many instances with real and certain benefit, in fact probably their action is chiefly that of a foreign protein any way. Vaccines of almost any character often produce excellent results. Of all of these bodies the typhoid vaccine, carefully given intravenously or given intramuscularly probably has the most striking effect, but it is probably necessary to give doses capable of producing marked reaction without which usually little benefit follows. Very marked and serious temperature reactions are often so produced and the judgment of the physician is sorely tried in deciding when to continue and when to discontinue these powerful agents.

Horse or other sera, specific vaccines or sera of all sorts can be used to good effect. Sterile milk is probably one of the safest of these and sometimes in spite of its usually inert character considerable joint improvement may follow. I know of no specific drugs except possibly the iodides which are of material and definite benefit in these phases of the disease, but in cases complicated by gout, atophan, colchicine and other colchicum

preparations are very often of material help.

Physiotherapy offers the most certain avenue of improvement in so far as the diseased joints, atrophied muscles and infiltrated tendons are concerned.

The physician must not become discouraged with these cases, and he must do all in his power to maintain full cooperation on the part of the patient for often painful procedures are demanded for very long periods of time. Too active, or the wrong sort of treatment may make the conditions worse, one joint may be showing marked improvement while another becomes worse on the same manner of treatment and often at the same time. An understanding of the mechanics of each joint, tendon and muscle must exist if maximum good result is to be reached.

Most of all, time is the great requisite. I have seen chronic cases discharged from my service after years of treatment, much of the time having been obligatorily spent in bed, but discharged finally to a degree of ability of self support really astonishing. Hydrotherapy is of value in many cases and visits to the various spas, particularly those under competent medical control, are now of great value. Although in the past the Europeans have greatly excelled us in this form of treatment, there are now developing in all parts of America institutions which accomplish results but little if at all inferior in these methods of treatment.

Little as we yet know of the utility of the various forms of radiation and light treatment, they possess even now possibilities which we are but slowly beginning to realize and profit from.

Back of it all we must continue to treat each case as an individual problem and perhaps beyond everything we must attempt by every means at our disposal the elimination from our list of those numerous conditions such as arthritis deformans, gout and other metabolic and trophic disorders which are differentiated only with the greatest difficulty from instances of chronic rheumatism.

Very great advances are being almost daily made in our understanding and treatment of rheumatism. Let us welcome every study and attempt in this direction; let us faithfully try out every theory in its clinical applications, meantime holding very fast to those drugs and measures which have in the past done us good service in this difficult field of medical therapeutics.

Purpuric Skin Manifestations Following the Use of Merbaphen*

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SINCE the introduction of merbaphen as an antisyphilitic agent and a diuretic much attention has been directed to its toxic effects. These have been, in general, indicative of mercurial poisoning, and include stomatitis, diarrhea, and renal irritation; minor toxic symptoms, such as slight fever, chills, malaise, and headaches, are common, but more severe reactions are relatively rare. Marvin has described something resembling a state of shock with chills, sweating, cyanosis, collapse, and occasionally urinary suppression following its use. Deaths have also been attributed to the drug (Redlich) not only when used as a diuretic, but as a remedy for syphilis. Nevertheless it seems to have been as well borne as any other mercurial preparation by most patients, and when one considers the condition of many of the patients who have been given the drug as a diuretic it seems remarkable that more evidence of its toxicity has not been observed. We have recently had under our care three patients in whom purpura appeared following its use, and one other patient in whom the drug may have been a factor in precipitating purpura. Since these purpuric manifestations apparently have not been described previously, it seems advisable to report these cases.

*Submitted for publication April 24, 1928.

REPORT OF CASES

Case 1.—An industrial executive, aged forty-eight, came to The Mayo Clinic in January 1925. He had used alcohol moderately for fifteen years. The presenting illness had begun with bronchopneumonia sixteen months prior to registration. At that time he noted slight enlargement of the abdomen, and somewhat later swelling of the feet. Within two months frank ascites and edema had developed. Four months later the abdomen had been tapped and a small amount of fluid removed. The patient had felt well except for the discomfort caused by the ascites.

General examination showed the patient to be slightly emaciated, and the abdomen greatly distended with fluid. There was considerable collateral circulation. The heart was somewhat enlarged and the heart tones were distant. The lungs were normal except for evidence of elevation of the diaphragm, and a few fine crackling râles at both bases. The systolic blood pressure was 115 and the diastolic 85; the pulse rate and temperature were normal. Urinalysis was negative except for a few hyaline casts.

The hemoglobin was 62 per cent (Dare), the erythrocytes numbered 3,750,000, the leukocytes 5,100. Two platelet counts were 98,000 and 106,000 respectively; the bleeding time and coagulation time of the blood were normal. The Wassermann reaction on the blood was negative. Tests of hepatic function with phenoltetrachlorphthalein showed dye retention graded 2. The serum bilirubin was 1.6 mg. for each 100 c.c. of blood. Electrocardiograms, roentgenograms of the chest, and tests of renal function were negative. A diagnosis was made of portal cirrhosis, and the patient was hospitalized for treatment with diuretics. He was placed on a diet low in salt and fluid, and the daily fluid intake restricted to 400 c.c. On the third day in the hosiptal he was given 1 c.c. of merbaphen intravenously. This was followed by a severe chill and a rise in temperature (103°F.). A slight erythematous blush appeared over the abdomen and a few purpuric lesions were noted on the legs at the time of the chill. Recovery was rapid and within a few hours the patient felt well. Significant diuresis did not appear during the day, and there were no other untoward effects of the merbaphen. The following morning the thighs and legs were covered with closely packed petechial hemorrhagic areas and the slight erythema noted on the previous day was somewhat deeper in color. A tourniquet test was positive. Three platelet counts on this day varied from 190,000 to 200,000. The bleeding time was fifty-five seconds, and the coagulation time four minutes and thirty-five seconds. The serum bilirubin was 1.9 mg. The urinalysis was negative for blood and bile. The mucous surfaces and retina were examined carefully for hemorrhages but none was found. The following day the patient felt much better and the purpuric lesions were fading rapidly. He expressed himself as being willing to go on with any treatment which we might suggest. Infected teeth were considered as a possible factor in the production of this unusual reaction, and it was decided to remove them. In the meantime ammonium chloride was begun in doses of 9 gm. daily. The teeth were extracted without incident, and the following day 0.5 c.c. of merbaphen was given intramuscularly. A fairly good diuretic response followed; the patient passed 1,100 c.c. of urine in twenty-four hours, and lost 3 pounds in weight. There were no further skin manifestations and the patient did not complain except of slight itching over the areas of skin previously involved, and a few urticarial wheals. The edema of the extremities had entirely disappeared and the abdomen was perceptibly softer. The urinalysis remained negative for albumin and red blood cells, and the serum bilirubin remained at 1.8 mg. for each 100 c.c. The tourniquet test was still positive, however. Two days later, since the patient had not had further symptoms of any consequence, merbaphen was repeated in a dose of 0.75 c.c. intramuscularly. The output of urine was 1,850 c.c., on this day; there was no reaction, and the patient felt perfectly well. Two days later merbaphen was again given (1 c.c. intramuscularly). The output of urine was 2,200 c.c. and the patient lost 5 pounds. At the end of this period of treatment the abdomen was free from fluid, and the collateral circulation had practically disappeared. The liver and spleen were definitely enlarged and palpable but other masses could not be found in the abdomen. The purpuric rash had faded.

The patient was dismissed from the hospital in good condition, and remained in good health for nearly a year thereafter without evidence of purpura, ascites, or edema. He died at his home a year later, presumably from gastro-intestinal hemorrhage; full details of his last illness are not available.

Case 2.—A farmer, aged sixty-one, came to The Mayo Clinic in August 1927 complaining of swelling of the abdomen and legs of about two months' duration. The appearance of ascites had been preceded by indefinite abdominal distress and occasional mild attacks of diarrhea. A history of alcoholism was obtained. The abdomen had been tapped once and a large quantity of clear yellowish fluid had been removed.

The patient was weak and rather pale and there was a slight icteric tinge to the skin and sclera. The systolic blood pressure was 92 and the diastolic 68; the pulse rate and temperature were normal. The abdomen was greatly distended with fluid and dilated veins were noted on the anterior abdominal wall. There was also moderate edema of the legs. The heart and lungs were essentially normal. Repeated urinalysis was negative except for a few hyaline casts. The hemoglobin was 65 per cent, erythrocytes numbered 3,650,000 and leukocytes 6,800. The Wassermann reaction on the blood was negative. The phenolsulphonephthalein return was 45 per cent in two hours, and the blood urea was 38 mg. for each 100 c.c. Roentgenograms of the chest were essentially negative except for elevation of the diaphragm and calcification of the aortic arch. Tests of hepatic function with bromsulphalein showed dye retention, graded 3. Serum bilirubin was 2.0 mg. for each 100 c.c., and gave an indirect van den Bergh reaction. Because of the patient's extreme discomfort, abdominal paracentesis was performed as an emergency measure, and 9,000 c.c. of amber-colored fluid was removed from the peritoneal cavity. Following this palpation did not reveal masses of any kind; the edge of the liver was palpable at the costal margin. Roentgenograms of the stomach and colon made on the two following days were negative. With malignancy excluded, a diagnosis of portal cirrhosis of alcoholic origin was made.

After paracentesis the ascites accumulated rapidly, and within a few days it was decided to resort to the use of diuretics. The patient was given ammonium nitrate, 6 gm. daily, and two trial doses of merbaphen, 0.75 c.c. intramuscularly and 1 c.c. intravenously, without any untoward effects. There was no significant increase in the urinary output. Following the second dose a few purpuric spots appeared on the dorsum of the left hand. A tourniquet test at that time was weakly positive. The following day a new collection of purpuric lesions was visible in the same area. The coagulation and bleeding time, and the platelet count were negative. On the following day the lesions were fading; the patient's general condition was otherwise unchanged. Because of the mildness of this reaction it was decided to repeat the merbaphen four days later and a dose of 2 c.c. was given intravenously. There was a slight diuretic response, 1,100 c.c. of urine being voided. Toxic effects were not noted, and careful search failed to reveal purpuric lesions. The second dose of merbaphen, 2 c.c., failed to produce either dieuresis or toxic effects. Calcium chloride in 2 gm. daily doses per os was also given at this time and the urinary output increased somewhat. On December 27, eleven days after the initial appearance of purpura, a dose of 2 c.c. of salyrgan was given, and was followed by a very good diuretic response, the patient voiding 2,700 c.c. of urine in twenty-four hours. The only toxic manifestation was another group of purpuric lesions on the dorsal surfaces of the hands. The patient's digestion and appetite were somewhat disturbed, which we attributed to the oral ingestion of ammonium nitrate and calcium chloride. Attempts at diuretic treatment were abandoned temporarily and the patient was placed on a bland diet. The ascites increased slowly, and since the patient had to travel a long distance to his home, tapping was resorted to.

It is significant that the blood urea in this case was slightly elevated, 43 to 46 mg., throughout most of the period of treatment, and the specific gravity of the urine remained at a level of 1.009 to 1.015 in spite of stringent fluid restrictions. It is probable that a mild degree of renal insufficiency due to renal arteriosclerosis was present.

This patient has returned to the Clinic, having again developed extensive purpuric lesions following a dose of merbaphen.

Case 3.—A merchant aged sixty-one came to the clinic in August 1927 with the characteristic history and symptoms of chronic diffuse nephritis. There was moderate edema of the extremities and face, and

definite cardiac enlargement. The systolic blood pressure was 220 and the diastolic 125. Ophthalmoscopic examination revealed mild retinitis of nephritis. Repeated urinalysis showed albumin, graded 2 to 3, and red blood cells, graded 1 to 3. The specific gravity of the urine ranged as high as 1.025. There was moderate anemia; the hemoglobin was 47 percent, the erythrocytes numbered 3,000,000, and the leukocytes 9,000. The phenolsulphonephthalein return was 15 per cent in two hours; the blood urea was 68 mg. and the creatinine 3.3 mg. for each 100 c.c. The blood cholesterol was elevated, the reading being 219 mg. for each 100 c.c. and the serum protein was low, 4.6 gm. per cent. The patient was under observation for about a month, improved somewhat, and returned to his home. He came back to the clinic three months later, more seriously ill than at the time of his first admission. The edema was extreme. Free fluid was present in the peritoneal and left pleural cavities. The systolic blood pressure was 180 and the diastolic 120. The results of laboratory examinations were much the same as on his first admission. The blood urea was 84 mg., and the creatinine 5.4 mg. for each 100 c.c. The kidneys still retained the ability to concentrate, as shown occasionally by a specific gravity of 1.022. The urine contained large quantities of red blood cells and at times gross hematuria was noted. After a week in hospital he was somewhat improved and it was felt that a trial dose of merbaphen could be given without undue risk.

A dose of 0.5 c.c. was given intramuscularly and produced a fairly definite increase in the hematuria, but no diuresis. There were no untoward effects, and a week later 1 c.c. of salyrgan was given intramuscularly. The hematuria was again somewhat increased but diuresis did not result. A week later the same dose of salyrgan was given again without any effect. Four days later the patient was given 300 c.c. of 30 per cent glucose solution intravenously on each of three successive days; with the last injection 1 c.c. of salyrgan was also given. This procedure did not increase the urinary output, and on the other hand did not cause ill effects other than vomiting on one occasion. Twenty-four hours after the last dose, purpuric lesions were noted on the dorsal surfaces of both hands. A tourniquet test was positive on that day and remained positive for several days thereafter. Observations of the coagulation factors of the blood, including platelet count, and clot retraction and prothrombin times, were negative. Only one collection of purpuric lesions appeared and these faded and disappeared within a few days. The patient remained under observation for about two months and slowly improved. At the time of his dismissal hematuria was still present but purpuric lesions or other hemorrhagic manifestations did not appear thereafter.

Case 4.—In this case, the relation of the purpura to merbaphen was suggested but not proved. This patient, an alcoholic man aged forty-nine, with the characteristic symptoms of portal cirrhosis and a strongly positive Wassermann reaction, was given several doses of merbaphen with potassium iodide and mercury rubs in an attempt to produce diuresis. Each dose was followed by a satisfactory increase in the urinary output, and toxic effects other than the presence of occasional red blood cells in the urine were not noted. Following the sixth dose of merbaphen, purpura appeared over the legs, and lesions of erythema multiforme were noted on the hands. All medications were discontinued at once and the skin lesions cleared up within a few days. Although merbaphen could not be excluded as an etiologic factor, the distribution of purpuric lesions was that which Knowles has described in mild iodide idiosyncrasy.

Discussion

As we have stated, we have not been able to find any previous reference to purpura resulting from the administration of merbaphen or salyrgan. In fact, cutaneous manifestations of any

kind seem to be infrequent. Zeiler, who had given 5,000 injections of the former drug to about 900 syphilitic patients, noted eruptions of the skin resembling those of the acute exanthemata (measles and scarlet fever) in 0.6 per cent of the cases. He did not regard these cutaneous reactions as due to an idiosyncrasy for mercury, since his patients subsequently tolerated other mercurials without symptoms, but rather felt that there was intolerance to the complex merbaphen molecule itself. Voigt, Levy-Lenz, and von Pezold (the last using merbaphen as a "mischspritze" with arsphenamine) did not mention cutaneous manifestations of any sort, in spite of the fact that they all had had a great deal of experience with the drug in the treatment of syphilis. Those who have used the drug as a diuretic do not mention purpura or lesions of the skin following its use. Other hemorrhagic manifestations have been recorded, however. Redlich, in describing three cases of fatal intoxication following merbaphen, mentions hemorrhagic encephalitis in two cases and renal hemorrhages in one case in which the history was suggestive of hemorrhagic disease, (possibly hemophilia). Kulcke noted hemoglobinuria in two cases after administration of merbaphen; he also found hemoglobin casts in the kidneys after death. Marcus mentions bloody urine and painful urination after two injections of the drug in a case of advanced cardiovascular-renal disease. Several observers have noted hemorrhagic lesions in the intestine with bloody diarrhea; the latter has not been uncommon in our experience.

The hemorrhagic lesions in the colon and kidneys suggest, of course, mercurial poisoning; the purpuric lesions are doubtless to be explained on the same basis.* Stelwagon and Pusey both asserted that mercurials may cause purpuric forms of dermatitis medicamentosa. Tomasczewski also mentioned this point in his extensive review of mercurial exanthemata, citing Fournier's case in which purpura developed after the administration of Van Swieten's liquor (a solution of corrosive sublimate) and Rosenthal's case in which mercurial inunctions produced similar lesions. Whether other portions of the complex merbaphen molecule (the double salt of sodium mercurichlorphenyl-oxyacetate with diethyl barbituric acid) are capable of causing purpura cannot be stated definitely.

Sollman, however, cited instances of exanthematous rashes caused by diethyl barbituric acid (veronal) and phenylethyl barbituric acid (luminal), while Jacobj has ascribed the toxic effects of the former substance to direct action on the wall of the capillary, comparable to that of arsenic. Possibly the combination of the barbituric acid molecule to that of mercury increases the tendency to capillary injury and purpuric manifestations.

It is noteworthy that the three cases described by us presented advanced renal or hepatic lesions, which have been considered by some authors to contraindicate the use of merbaphen. Saxl counsels against the administra-

*B. T. Johnstone and H. M. Keith have shown that the toxic dose of merbaphen in rabbits is closely related to its mercury content. (Unpublished data.)

tion of the drug in renal disease, and Mühling believes that it may injure the liver in certain types of cirrhosis. Schurr, citing his own experience and that of Kollert, makes the interesting observation that the likelihood of mercurial poisoning after the administration of merbaphen is in inverse proportion to the degree of diuresis obtained. He believes that under ordinary conditions merbaphen is rapidly excreted by the kidneys as such, but that if renal insufficiency exists, excretion is retarded and the mercury released by the slow disintegration of the merbaphen molecule is able to exert toxic effects. The application of this hypothesis to the cases which we have described is obvious.

In spite of the contraindications for the exhibition of merbaphen laid down by the German writers there has been a tendency on the part of many American investigators to extend the use of the drug as a diuretic to many advanced types of hepatic and renal disease associated with ascites and edema. The experience of The Mayo Clinic with merbaphen and salyrgan seems to indicate that if they are used cautiously in hepatic disease untoward effects rarely follow and that in many cases of nephrosis or diffuse nephritis in which renal function is fairly good, they may be successfully employed with little danger of serious renal injury. The purpuric lesions in our cases were unattended by generalized bleeding or other signs of severe constitutional injury; they subsided spontaneously and did not appear to be of great significance to the patient's general health. It must be remembered that purpura is frequently encountered in advanced renal and hepatic disease independent of the treatment employed; it is quite probable that mercurial diuretics merely bring out these lesions in conditions in which a latent tendency to capillary bleeding already exists. It will be noted that a positive tourniquet test was encountered over a period of several days in all of our cases, a point which would seem to show but slight widespread capillary injury. The possibility comes to mind that merbaphen may exercise its effects as a diuretic by action on the capillary epithelium. It may be that when the drug causes purpura it is exercising its usual effect but exercising it on capillaries injured by disease. Considered in this light, it seems probable that when purpura appears after the use of merbaphen it may possibly be an expression of the underlying disease as well as evidence of a true toxic effect of the drug.

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The Extra-Cerebral Causes of Epilepsy*

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A NEUROLOGIST is consulted perhaps more frequently in regard to epilepsy than any other disease. At least, that has been my experience. Therefore the subject of the extra-cerebral causes of epilepsy is not without interest. As a preparation for this paper one of my assistants looked up the subject in various text books and more recent papers, and the number and variety of causes is astonishing. From this list it would seem that any cause may produce fits, for every disease and every possibility has been mentioned in the literature.

In view of this fact I thought it would be interesting to consider the causes of epilepsy as they are given in the literature on the subject and analyse them in the light of my own personal experience.

Broadly speaking the extra-cerebral causes of epilepsy can be classified as follows:—

1. Toxic states.
2. Reflex causes.
3. Infectious diseases.
4. Circulatory disorders.
5. Respiratory disorders.
6. Endocrine disorders.

1. Toxic States:

I. Toxic states arising in Viscera:

(1) Intestinal disorders—kinks in the colon, malposition, adhesions, colonic stasis.

(2) Disorders of the stomach—overeating, overloading the stomach, eating indigestible foods; idiosyncrasies for certain foods.

(3) Intestinal putrefaction.

(4) Kidney disorders—uremia, chronic renal disease without uremia.

II. Toxic conditions arising from the ingestion of poisons:

(1) Alcohol—chronic drinkers, especially of whiskey and absinthe.

(2) Miscellaneous poisons — lead, cocaine, arsenic, antipyrin, strychnine, chloroform, ether, camphor monobromata, theophyllin, stovain in lumbar anesthesia.

2. Reflex Causes:

(1) Nasal disorders—adenoids and nasal polyps, diseases of the accessory nasal sinuses.

(2) Throat disorders—diseased tonsils.

(3) Ear disorders — foreign bodies in the ear and

*Read before the American College of Physicians, New Orleans, March 7, 1928.

chronic otorrhea; pressure of an aural polyp.
(4) Teeth—carious and impacted teeth, apical abscesses; dentition.
(5) Menstrual disorders.
(6) Pregnancy.
(7) Masturbation.
(8) Intestinal worms—various parasites such as hookworm, taenia solium or saginata, taenia echinococcus.

3. Infectious Diseases:
(1) Scarlet fever.
(2) Pertussis.
(3) Typhoid fever.
(4) Measles, influenza, smallpox, malaria, yellow fever, vaccinia.

4. Circulatory Disorders:
(1) Embolic disturbances, cardiac failure.

5. Respiratory Disorders:

6. Endocrine Disorders:

Toxic States

Toxemias are perhaps most frequently mentioned as causes of epilepsy, for it is commonly supposed that disorders in the viscera can bring about convulsions, and yet in my own experience I have never seen fits occur in an adult resulting from disturbances of the stomach and intestines. It may produce fits in children. I remember a baby about seven days old who had typical Jacksonian convulsions, in whom there was a kink in the colon. In common with other physicians I have seen fits in children presumably brought about by over-eating or by so-called intestinal putrefaction, but I have always felt that in most of these children there is a spasmophilic condition or a tendency for fits. My experience has been that if a child has a real epileptic attack, no matter from what cause, that child is an epileptic. I am aware this is not the usually accepted point of view, but nevertheless, that has been my experience. Many fits are diagnosed as epileptic in which there is no loss of consciousness. It also depends on what one chooses to call epilepsy. I do not diagnose epilepsy unless there is either an impairment or loss of consciousness.

Of course, in uremia epileptic attacks may occur, but that is because in uremic conditions there are definite organic changes in the cerebral cortex. Years ago I reported a case of hemiplegia with convulsions complicating a uremia, in which I was able to demonstrate by the Marchi stain secondary degeneration in the pyramidal tracts.

Toxic Conditions arising from Poisons: I have seen epilepsy occur in chronic alcoholics and I believe that this can occur. In the literature are found accounts of epilepsy developing in heavy wine, whiskey and absinthe drinkers. The infrequency of epilepsy amongst Jews has been attributed to the lack of chronic drinkers in this race. However, in my own experience I have seen only a few instances of epilepsy in alcoholics, but I have the impression that this is probably because they have already been epileptics.

The various miscellaneous poisons, such as lead, cocaine, arsenic, strychnine, chloroform and so on, are mentioned as causes, but they have not occurred in my experience and I doubt

that they are real causes of the disease.

Reflex Epilepsy

Opinions differ as to reflex epilepsy. Two such distinguished neurologists as Oppenheim and Gowers have opposing points of view, the former stating that it is relatively a frequent cause, and Gowers that it occurs only in those with an epileptic disposition.

Amongst the reflex causes which are commonly given, are disturbances in the nose and throat. Adenoids, polyps and diseased tonsils have been given not only as the cause of epilepsy, but of every disease known to medical science, and their removal has been hailed as a cure-all, but this has not been my experience. The same thing is true of diseases of the accessory sinuses and of ear diseases.

So far as carious teeth and apical abscesses are concerned, I can only say that I have never seen the removal of apical abscesses cause a cessation of epilepsy. One of the traditions in our profession is that dentition in children may cause convulsions, and there is no denying that the irritable condition which these children get into is frequently accompanied by a convulsion, but my own thought has always been that such children belong to the spasmophilic group or are really cases of epilepsy.

I have never been able to trace the relationship between the menses and epilepsy, although no doubt numerous authors can martial many facts to disprove this statement. Neither can I see any relationship between pregnancy and epilepsy. I have seen instances in which attacks have either diminished or increased during the pregnant state.

Sexual abuses such as masturbation have been given as frequent causes of convulsions, but I have never been able to trace the direct relationship between the two.

Intestinal worms are commonly given as causes of fits in children. In the south the hookworm is supposedly a common cause of convulsions, and it is not clear whether they are caused by direct invasion of the brain by the worm, or whether they are caused by a cerebral edema. I doubt this cause and when it occurs believe that these patients have epileptic tendencies.

Infectious Diseases

In acute infectious diseases convulsions do occur. This is true in scarlet fever and pertussis, but in these two conditions cerebral complications are probably the basis for such involvement. Such infectious diseases as typhoid fever, measles, influenza, smallpox, malaria, yellow fever and vaccinia are given as causes, but I believe when convulsions occur it is due to a direct cerebral involvement, or the subject of the attack is probably predisposed to the disease.

Circulatory and Respiratory Disorders

Different cardiac conditions as well as respiratory diseases are mentioned in the literature, but again this has been contrary to my experience.

Endocrine Disorders

In the last few years it has been the fashion to ascribe dysfunction of the different glands as a cause of con-

vulsions. This has been particularly true as regards the pituitary gland. The sex glands have also been accused but to a less extent, and no gland has escaped. There is no doubt that in a great many epileptics there is a dysfunction of the glandular system. In my experience epilepsy is not uncommon in dyspituitarism, but I have never been able to trace the cessation of attacks to endocrine therapy, although the literature is full of it.

Summary

It is obvious from the above that particularly in children, there occasionally occur epileptic attacks in which toxic or reflex causes may be found, removal of which may cause a cessation of convulsions. Nevertheless, it is my belief that such children either belong to the so-called spasmophilic group or are definitely epileptic. By the spasmophilic, I mean, a type of individual in whom there is a tendency to convulsions whenever the body functions are not working in harmony. The probabilities are that the majority of such children are potentially epileptic, and that during the rest of their lives future attacks may develop if some untoward condition develops in the body.

The convulsions which occur in infectious diseases are probably the result of definite organic changes in the cerebrum, for encephalitic complications are not unusual, particularly in scarlet fever and whooping cough.

In adults convulsions may complicate such conditions as alcoholism, uremic states, poisons and so forth. They are probably the result of direct involvement of the cerebrum or else they occur in an individual who either had epilepsy in childhood or has definite epileptic tendency.

I do not believe that the removal of adenoids, polyps, diseased tonsils or teeth will cure epilepsy.

I do not mean to infer from the above that foci of infection should not be removed. It is obvious that anything which will better the patient's physical condition will in the majority of instances cause a diminution of the number of attacks, but I have never seen the removal of any foci *cure* epilepsy.

Conclusion

Strictly speaking, there are no extra-cranial causes for epilepsy. Whenever convulsions occur from so-called toxic, reflex or other causes, it is because the subject of the attacks has either a tendency to epilepsy or is an epileptic.

Editorial

ACUTE RHEUMATIC FEVER

To any one interested in coincidences the fact that in different parts of the world during the last year four independent Congresses or Symposia on Rheumatic Fever were announced may seem rather remarkable. The fact is interesting enough in indicating the important position held in the medical mind by this disease. The reasons for this are obvious. In the first place is the wide-spread interest in the propaganda for the prevention of heart-disease which has advertised rheumatic fever as one of the most important etiological factors of cardiac disorders. Some cardiologists are so impressed with this idea that they can hardly see anything but "rheumatism" as the essential cause in their cardiac cases. It really does not matter to them whether the patient gives a definite history of rheumatism or not. Any seriously decompensated heart, whether with valvular involvement or without, is at once dubbed "rheumatic"; and as there are few adults in this world, who at some time or other, have not had occasional pains or aches in muscles and bones, positive questions along this line practically always elicit a confirmatory clinical history of rheumatism. Serious mistakes of this kind are particularly frequently made in the non-valvular cases, since syphilis is so frequently the etiologic factor in these. In the case of a young adult male with serious cardiac decompensation without mitral or aortic valve involvement syphilis is the first thing to be considered as the possible etiological factor. Nevertheless, such a patient will practically always, on being questioned, give a clear history of "rheumatism" and that settles the matter for the clinician who forgets, or more likely never has known, that there is such a thing as "syphilitic rheumatism". The history of joint or bone pains, *usually more severe at night*, in these cardiac cases should be confirmatory of syphilis and a syphilitic heart, not of a rheumatic one. Further, it is just in these syphilitic rheumatic cases that antisyphilitic treatment may be of some avail. Another fact, usually not recognized by the internist, is the association of "rheumatic" pains with the Graves' constitution. The goiter heart is again, under such circumstances, considered a "rheumatic heart". The difficulty is that we do not know exactly what *rheumatism* is, and are dealing with a varied group of pathologic conditions of different etiology producing the same or similar clinical phenomena. There are *different forms of clinical rheumatism*, but we are not yet clinically able to differentiate these exactly or to show their relationship to definite etiologic agents. We do not even know the cause of the most clearly defined clinical form of rheumatism, namely, acute rheumatic fever. This form

does seem to have a definite clinical entity. It begins usually during the school age, five to sixteen years, with rather obscure symptoms of nervousness, twitchings, "growing pains", pallor, shortness of breath, increased susceptibility to sore-throat or tonsillitis, dental infections, etc. Such symptoms may be only those of a *susceptibility* to acute rheumatic fever, or they may represent the actual beginnings of the disease. At any rate, out of such prodromal or early symptoms there follows all too frequently the fully developed symptomatology of polyarthritis, pancarditis and chorea. As to the etiologic agent itself, we are still in doubt. At the rheumatic fever symposium of the Association of American Physicians held in Washington, May 2, Riesman and Small presented the evidence for *Streptococcus cardioarthritidis;* Kinsella for *St. hemolyticus* as producing characteristic joint-lesions in rabbits; while at the Bath Congress, in England, a week later, the general consensus of opinion was that *St. viridans* was the infective agent. One advance of importance made at the Washington meeting was the work presented by Swift and his associates of evidence in support of a theory that the general body reaction in rheumatic fever is allergic in nature, probably allergic to a non-hemolytic streptococcus. The type of allergy is that of a bacterial toxin allergy and not serum disease allergy; and is similar to that seen in tuberculosis and syphilis. A focus is necessary to produce a state of allergy; and a patient will not improve until the focus of infection has been removed. The use of vaccines in patients, without giving salicylates, produced very stormy reactions. The varying morphologic and cultural characters of the streptococci obtained from human cases of rheumatic fever are so diverse that at the present time, we must regard the etiology as still unsettled. Those who do not accept the streptococcus hypothesis are inclined to compare the clinical course and pathology of the rheumatic disease with the chronic and latent infections produced by the higher organisms of tuberculosis and syphilis. Bezançon and Weil look upon the affection as a chronic cardiac disease with successive attacks involving the serous system. They hold that we should not consider the disease as consisting of a series of acute lesions but as a true chronic disease that may remain latent for many years, as do tuberculosis and syphilis. In the joints the lesions appear very active, acutely inflammatory and transitory; in the heart the lesions are of a chronic nature, warty, nodular, cicatricial, indurative. The rheumatogenic organisms have a particular tendency to the production of cicatricial tissue. The state of the myocardium in chronic cases may be interpreted as showing that the chief reservoir of the rheumatic virus is in the heart—the endocardium, the pericardium, and particularly in the myocardium. The French school sees a closer analogy between the rheumatic heart and syphilis or tuberculosis of the myocardium, than it does to the pathology of the lesions produced by the pyogenic organisms, gonococci or streptococci. As to the nature of the so-called Aschoff nodule nothing decisive has been gained from the recent symposia. The French school does

not regard them as true infective nodules comparable to those of tuberculosis, but considers that they represent a nodular inflammatory process completed or complicated by a giant-cell proliferation of the striated muscle cells of the myocardium, following the separation of the myoblastic elements. This view has also been held for some years by certain American pathologists.. The nature of the cardiac lesions needs careful study; this should at least be one phase of the rheumatic fever problem that morphologically at least should be relatively easily cleared up. At the Washington meeting von Glahn and Pappenheimer made an important communication on the lesions found in the auricle and blood vessels in rheumatic fever, but this has not yet been published. Inasmuch as the American Association of Pathologists and Bacteriologists has announced a Rheumatic Fever Symposium for its meeting next year, it is hoped that some more decisive light will be thrown upon the nature of rheumatic fever primary lesions. Not much new information has been offered by the various symposia as to the clinical pathology or the physiologic chemistry of the disease. The study of the blood pH and the alkali reserve shows that these are normal in rheumatic patients. This is of interest in relation to the old conceptions of increased acidity of the blood in this disease. The ionic acidity of the urine also remains normal. There is, however, an increase in the amount of fibrin in the blood, equalling that found in pneumonia (10-12 g. of fibrin per liter of plasma). Although the hyperinosis of rheumatism is of no value in differential diagnosis, it has prognostic value, in that it is proportional to the severity of the case. The more severe the acute joint lesions, the higher the fibrin content of the blood. As long as the fibrin value of the blood does not return to normal it is advisable to continue the administration of salicylates. The pallor of rheumatic patients in many cases is not due to anemia. Many of these cases are ochrodermic rather than anemic. At the time of the acute attack there is often a polynuclear leucocytosis of 13,000-16,000; this disappears as the inflammatory symptoms diminish. In cases without inflammatory symptoms there may be a transient mononucleosis. No innovations in treatment have been brought out in any of the discussions. Methods of prophylaxis are still hypothetical; dampness is not an environmental factor of prime importance as was once thought. Cases are more numerous today in urban life than in rural. In children the disease is, however, largely dependent upon the environment—anything that lowers the general resistance, such as poverty, urbanization and industrialization. In resistant cases a 5 per cent mixture of sodium salicylate in 10 percent glucose is used for intravenous injections. We are still in doubt, however, as to whether sodium salicylate has the same effect on the cardiac involvement as it has on the joint symptoms. In this relationship the question of allergy is signicant. One thing strongly brought out at the Bath Congress is the tremendous economic importance of this disease, particularly for England. The estimated cost of rheumatism in England in 1927 among the

insured wage earners was £17,000.000. This great sum represents approximately the yearly disbursements under the national health insurance scheme to insured persons on account of rheumatism together with the accompanying loss of wages. It does not include any sum for the cost of medical treatment of persons suffering from rheumatism who are not totally incapable of work, of the cost of nursing in bad cases nor does it take into account the cost of any institutional treatment. Further, it does not cover fully persons over 70 years of age; nor did it make any allowance for the dependents of insured persons, all of which should be considered if the total cost of rheumatism to the country is to be given terms anything like its full value. With such economic facts at hand it is no wonder that a psychologic state concerning rheumatism should have developed throughout the civilized world, and given rise to coincident congresses and symposia on this important disease.

Committee on Research in Syphilis

Incorporated

370 Seventh Avenue, New York, N.Y.

On March 10 and 11, 1928, a group of public spirited laymen, acting through Doctor Edward L. Keyes, President of the American Social Hygiene Association, invited a group of syphilologists and investigators interested in syphilis, to meet at the Hotel Plaza, New York City, for the purpose of organizing the Committee on Research in Syphilis.

While the importance of syphilis is well known to the medical profession, large funds for the systematic study of the disease have, with the exception of the government appropriations during the war, been exceedingly difficult to obtain. The Committee on Research in Syphilis will distribute annually through its sub-committees, the funds made available by the group of donors, to subsidize and develop research in both the clinical and laboratory aspects of the disease.

It is the purpose of the Committee to expend the sums placed at its disposal in the development of a constructive program of research with planned activities and selected cooperators; and upon the stimulation through grants of researches already in progress or about to be undertaken. There will be for the present, at least, no investment in plant.

The form of organization adopted was as follows:

The scientific and medical members of the Committee on Research in Syphilis form the General Advisory Committee, with an initial membership as follows:

General Advisory Committee: Dr. John H. Stokes, Chairman; Dr. W. J. M. A. Maloney, Secretary, Room 1545, 370 Seventh Ave., New York City; Dr. Wade H. Brown, Dr. Walter M. Brunet, Dr. Alan M. Chesney, Dr. Harold N. Cole, Dr. C. W. Field, Dr. Reid Hunt, Dr. H. G. Irvine, Dr. P. C. Jeans, Dr. R. L. Kahn, Dd. Edward L. Keyes, Dr. John A. Kolmer, Dr. W. G. Lyle, Dr. J. E. Moore, Dr. Alfred T. Osgood, Dr. Thomas Parran, Jr., Dr. Albert Pfeiffer, Dr. J. F. Schamberg, Dr. William F. Snow, Dr. H. C. Solomon, Dr. Homer F. Swift,

Dr. Carl Voegtlin, Dr. Aldred S. Warthin, Dr. J. S. Wheelwright, Dr. J. J. Wile, Dr. Linsly R. Williams.

The actual business of the group will be divided between a Finance Committee including the donors, and an Executive Committee, with membership as follows: Dr. Edward L. Keyes, Chairman; Dr. W. G. Lyle, Dr. W. J. M. A. Maloney, Dr. Alfred T. Osgood, Dr. William F. Snow, Dr. Homer F. Swift, Dr. J. S. Wheelwright.

The recommendation for grants will be made by the Scientific Committee to the Executive Committee after appropriate investigation.

The Scientific Committee comprises: Dr. John H. Stokes, Chairman, Professor of Dermatology and Syphilology, School of Medicine, University of Pennsylvania, Philadelphia; Dr. W. J. M. A. Maloney, secretary, Commissioner in Lunacy, New York State, Consulting Neurologist, New York City Hospital; Dr. Howard T. Karsner, Chairman, Division of Medical Sciences, National Research Council; Dr. Thomas Parran, Jr., Assistant Surgeon-General, U. S. Public Health Service; Dr. William F. Snow, General Director of the American Social Hygiene Association; Dr. H. N. Cole, Professor of Dermatology and Syphilology, Western Reserve University (Rotating Member); Dr. Udo J. Wile, Professor of Dermatology and Syphilology, University of Michigan (Rotating Member).

The organization of the Scientific Committee permits of the calling of experts in special fields of syphilology to meet with the Committee in conference on questions both of general policy and expenditures to be recommended; final decision as to expenditures rests with the Executive Committee.

All who are interested in any aspect of syphilology are cordially invited to send to the Chairman of the Scientific Committee pertinent suggestions as to problems to be undertaken, together with the names and records of investigators of promise.

Applications for grants should for the present be addressed to Dr. John H. Stokes, Chairman, Scientific Committee, 3800 Chestnut Street, Philadelphia, Pennsylvania.

Further particulars in regard to the method of granting subsidies and the policies of the Committee will be sent on request, together with application forms. Applicants are requested to state in their first communication whether the problem to be undertaken is of a clinical or laboratory character, or a combination of the two.

Abstracts

Fish Tapeworm. Intestinal Infection in Man: The Infestation of Fish in Manitoba Lakes. By DANIEL NICHOLSON (The Canadian Medical Association Journal, July, 1928, p. 25).

The records of the Winnipeg General Hospital show 15 cases of fish tapeworm infestation duirng the past four years, five of these occurring in 1927. Three of the cases presented an associated anemia, one being of the pernicious type. The patients were chiefly Russians or Finns, and the majority had not been in this country very long. Only one patient, a child of 11 years, of Scottish extraction, was native-born. It was considered that two of the cases probably had the tapeworm before coming to this country. Jewish women but no Jewish men were among the cases. An examination of fish obtained from Lakes Winnipeg and Manitoba showed the presence of larval forms of the fish tapeworm in pike and pickerel, but in no other forms. Seven out of thirty-five pike examined from the two lakes were infested with fish tapeworm larvae, as shown by feeding the larvae to dogs and producing the adult tapeworm in the latter. Two out of seven pickerel were similarly infested. Descriptions and illustrations of the pleroceroids and adult worms are given, with details of the feeding experiments. Vergeer's experiments made in Ann Arbor were fully confirmed. The latter worker had already demonstrated the presence of plerocercoids in fish imported into the United States from Lakes Winnipegosis and Manitoba. This paper is another link in the chain of evidence showing the rapid and widespread infestation of the fresh-water fish of the northern states and Canada with this parasite.

Aortic Insufficiency Due to Rupture By Strain of a Normal Aortic Valve. By C. P. HOWARD. (The Canadian Medical Association Journal, July, 1928, p. 12).

Rupture of the healthy mitral and tricuspid valves due to injury from external causes has been known to pathologists since the time of Marat and Corvisart, but the earliest recorded case of rupture of the aortic valve is one by Plenderleath in the *London Medical Gazette* for 1820. In a careful search of the literature Howard has found but 112 cases, to which his own case added makes 113, of instances of rupture of a healthy or diseased aortic valve from muscular effort or trauma. Since the textbooks and reference works of the day practically ignore this condition or refer to it as a very rare cause of aortic insufficiency, Howard has made a careful and thorough analysis of the reported cases and has condensed the facts presented by them in this article. His own case was that of a large, stout French-Canadian male, 33 years old, a chauffeur, who after cranking his car for two minutes was suddenly seized with a sharp pain in his left upper chest and in his epigastrium, but with no radiation to the arm; he immediately became short of breath and began to cough, and was obliged to give up work because of the pain and the dyspnea. Subsequently he noted a "thrill" in the left upper chest. After remaining in bed for two weeks he returned to work but was obliged to discontinue it, as his symptoms became very acute. The pain then radiated down the left arm, and even down the left leg. He became very orthopneic and constantly vomited. His feet became edematous. His course was a progressive downhill one, and death took place from cardiac decompensation twelve weeks after the muscular strain. At autopsy the heart showed marked hypertrophy and dilatation; the common attachment of the anterior and me-

dial (left posterior) cusps of the aortic valve was torn away from the aortic wall, due to a transverse tear in the intima, five-eighths of an inch in length, allowing the cusps to become very lax. Microscopically the cusp was normal, and no evidence of syphilis was found about the vasa vasorum of the aorta. Of the 113 cases now recorded of rupture of the aortic valve only 49 were proved by autopsy. When classed as "strain" and "traumatic" groups, the strain group is the larger, comprising 30 proven and 30 unproven cases, as compared with 14 proven and 33 unproven in the traumatic group. In 5 acceptable cases the cause of the rupture was not stated. The majority of the "strain" group were observed in Great Britain; while Germany led, with France as second, in the number of "traumatic" cases. Only one female is listed among the "strain" cases and that one doubtful; while in the "traumatic" cases there were three females, two of which were not proven. The male sex is, therefore, much more exposed to rupture of the aorta than the female. The fourth and fifth decades of life were the most susceptible; the mean age in the strain group was 37.2 years, in the traumatic group 45.6 years. As to occupation, 81 per cent of the cases in the strain group occurred in occupations exposing the patient to great muscular effort. In the traumatic group 80 per cent of the proven cases occurred in individuals whose occupations exposed them to injury. In the unproven group the occupation in the majority of cases was of an arduous nature. Here the commonest cause of injury was a fall, while blows from a blunt instrument and a crushing injury to the chest were next in frequency. As to the previous medical history, alcoholic excess appeared to play no important rôle, either in the strain or traumatic group. In the strain group syphilis does not appear as prominently as one might expect; and in the 14 proven cases of the traumatic group there is no case of known lues. A history of rheumatism, chorea and tonsillitis was present in 5 cases, negative in 11 and not mentioned in 14 of the proven strain group. In only 7 of the entire group of 60 cases was there presumably a previous rheumatic endocarditis. In the traumatic group there was no case with a history of the rheumatic cycle among the proven cases; in the unproven group there were only four who possibly had an aortic valve damaged by a previous attack of rheumatism. Only a small minority of the cases of both groups had a history of any previous cardiac symptoms. The most frequent single cusp to be involved is the anterior, next the right posterior, closely followed by the left posterior; when torn in combination with one or two other cusps the anterior is still first, right posterior next and the left posterior last. This is contrary to the earlier teaching that usually the posterior cusps are torn, but corresponds with the experimental results of Barié. In the muscular strain group the angle of attachment on the intima of the aorta near its base is more likely to be ruptured, while in the direct traumatic cases the cusp itself is more apt to be injured. In only 13 of the 48 autopsies (27 per cent of the whole series) was the aortic valve reported as absolutely normal, but it was more frequently normal (44 per cent) in the traumatic group than in the strain group (23 per cent). In the great majority of the protocols the aortic valves are described as thickened, atheromatous or even calcareous. In 2 cases there was evidence of a fresh endocarditis in addition to the rupture, but in both it was probably of more recent origin. In general, the aorta was much more frequently the seat of atheroma in the strain group (16 cases) than in the traumatic. Hypertrophy of one or both ventricles was the rule, frequently associated with dilatation. The usual pathological picture of cardiac decompensation was found in many of the cases. Muscular effort or strain resulting in rupture of a healthy valve was shown only 7 times in the series; and is, therefore, a rare event. In a valve previously the site of rheumatic or syphilitic disease rupture of an aortic cusp is more likely to occur, and many authorities recognize only this group. Many of the case reports are so lacking in detail of microscopical

changes that the negative reports are more or less doubtful. The characteristic symptoms of rupture of the aortic valve are pain, syncope or vertigo, oppression and dyspnea, palpitation and hemoptysis, sensation of roaring in chest, neck or ears, and finally the usual signs of aortic incompetency. A murmur was audible to the patient or his friends in 19 of the strain series and 4 of the traumatic. In some of the cases a systolic murmur and thrill were also present at the base, and it has been suggested that this is due to the torn segiment floating in the blood stream. A diagnosis is possible if the previous condition of the heart is known, but without an autopsy this cannot be regarded as conclusive. The prognosis depends upon the size of the defect and the condition of the heart muscle. An immediate fatal syncope may result, or death may take place weeks or months later. This is the most common course. In a few cases the lesion has apparently healed, and no serious symptoms resulted until years later. Cases of chronic aortic insufficiency have been reported in which autopsy showed repair of a small tear. The duration of life may then vary from a few hours or days to several years, the average being about eighteen months. The prognosis appears to be better in the traumatic cases, the mean duration for this group being forty months for those who survive the trauma. In the event of a suspicion of rupture of an aortic valve from strain or rheumatism, the indications are first absolute bed-rest in an effort to avoid all causes likely to give rise to inflammation of the valve, and second to subdue such symptoms as may arise. Great caution in exercise and an avoidance of all forms of excitement and the use of depressant agents must be insisted upon. Peacock strongly advises against the use of digitalis. Usually an ice-bag to the percardium, and possibly venesection will relieve the patient. Later, purgation and diuresis may be tried.

Angina Pectoris. A Syndrome Caused by Anoxemia of the Myocardium. By Chester S. Keefer and William H. Resnik (Archives of Int. Med., June, 1928, p. 769).

Although angina pectoris has been known for over a century and a half there is still a lack of unanimity regarding its cause. The authors give a very complete discussion of the symptomatology, pathogenesis, and pathology with a critical review of the prevailing theories of the pathogenesis, their chief effort being to prove that the condition described by Heberden has a definite and single cause, anoxemia of the heart muscle. "There is only one angina pectoris, the angina pectoris due to anoxemia of the myocardium. All others are false." So the authors paraphrase the aphorism of Huchaed, substituting the word anoxemia for coronary disease. Their conclusion is that a critical analysis of the theories that attribute angina pectoris to coronary spasm, to disease of the aorta or to myocardial exhaustion demonstrates that these views are open to such serious criticism that they become unacceptable; on the other hand, it can be shown that anoxemia of the heart, in the sense in which they have employed the term, explains every characteristic of angina, including the likelihood of sudden death, which must be considered an integral feature of the condition. The percentage of cases in which conditions capable of producing anoxemia of the myocardium have been found in cases of undoubted angina is so high that the accuracy of the diagnosis in the few remaining instances seems open to question. They feel that an eclectic theory which admits a varied basis for origin should be abandoned. The angina of Heberden has but one cause, anoxemia of the myocardium. The pathologic conditions associated with angina pectoris may be grouped as follows: 1, Coronary disease, sclerosis with or without complete obstruction, occlusion or encroachment of the mouths of the coronary arteries by syphilitic aortitis or arteriosclerosis;; 2, aortic insufficiency; 3, miscellaneous conditions. Coronary disease and aortic insufficiency make up the vast majority of cases. As far as syphilis is concerned the authors believe that uncomplicated syphilitic aortitis never causes

angina, but that when angina occurs in a case of syphilitic aortitis, there is also present coronary disease or aortic insufficiency. The aortic involvement usually found in association with angina is purely coincidental; it happens to be associated frequently with the lesions that are responsible for the latter. Although coronary disease or aortic insufficiency, or both, are usually present in angina there are exceptional cases associated with other conditions producing anoxemia of the heart, such as anemia, arteriovenous fistula, pericarditis, and mitral stenosis. When the facts are complete it is possible to demonstrate in every case of true angina pectoris conditions capable of producing anoxemia of the myocardium.

Reviews

Lobar Pneumonia. A Roentgenological Study. [A Correlation of Roentgen-Ray Findings with Clinical and Pathological Manifestations]. By L. R. SANTE, M. D., F. A. C. R., F. A. C. P., Associate Professor of Radiology, St. Louis University School; Radiologist to the University Group of Hospitals (St. Mary's Hospital and Infirmary); Chief City Radiologist to St. Louis City Hospitals; Consulting Radiologist Koch Hospital for Tuberculosis, St. Louis Training School, etc. With a Foreword by James T. Case, M. D., F. A. C. S., Battle Creek, Michigan. 137 pages, 43 illustrations. Paul B. Hoeber, Inc., New York, 1928. Price in cloth, $3.00.

This monograph, as pointed out by Dr. Case in his Foreword, marks another important step in the evolution through which roentgenology has been passing. From its earliest application in the diagnosis of fractures and bone diseases, and the localization of opaque foreign bodies, projectiles and calculi this branch of medical science has developed into one of the most important aids in the diagnosis of internal disorders. Roentgenological assistance is now generally sought in the diagnosis of gastro-intestinal, cardiac and pulmonary diseases, and constantly new researches in various fields of surgery, internal medicine, obstetrics, etc., are being carried out. The epidemics of 1918 and 1919 served to demonstrate beyond any doubt the great usefulness of roentgenographic examination in diseases of the lungs. Being impressed by the accuracy and comprehensiveness of the knowledge obtained in cases in which the physical signs and the other methods of examination in general use were of little value in forming an estimate of the character of the pathology present, the author began a roentenographic study of lobar pneumonia in the winter of 1919. During the past seven years this study at the St. Louis City Hospitals and the St. Mary's Hospital group has embraced 1,188 cases. These studies showed that while an initial peripheral involvement of the lung was the type most frequently seen in children, it was rarely, if ever, the type of involvement seen in adults. With the information conveyed by serial film examination it was often found possible to detect beginning complications before they could be detected by other means. Serial roentgenographic examination naturally suggested itself as a valuable means for checking the progress of the lesion in the experimental investigations of diseases of the lung. The chapters consider respectively the etiologic factors, pathology, method of inoculation and spread of the organisms, roentgenographic characteristics, course of the disease, method of onset in children, unusual types of development, hilum pneumonia, pulmonary complications, prognosis, and differential roentgen-ray diagnosis, with discussion, references and index. The monograph is of course built around the illustrations. These are all very good, and are very well reproduced. They all tell the story they are expected to, and do not leave the reader in doubt. Altogether they form a most valuable roentgenographic study of lobar pneumonia and will serve as a standard for comparison with the films from any given case. They demonstrate successfully how much information as to the localization and course of the pneumonic process can be furnished by roentgenographic examination, and prove the great value of this new application of the X-ray in diagnosis.

Clinical Aspects of the Electrocardiogram. A Manual for Physicians and Students. By HAROLD E. B. PARDEE, M.D., Assistant

Professor of Clinical Medicine, Cornell University Medical School; Assistant Attending Physician, New York Hospital; Consulting Cardiologist, Lying-in Hospital and Woman's Hospital, New York City. Second edition, revised. 242 pages, 60 illustrations. Paul B. Hoeber, Inc., New York, 1928. Price in cloth, $5.50.

The first edition of this book was published in June, 1924. Since that edition no new basic principles in the clinical use of the electrocardiogram have appeared. It has become increasingly evident, however, that this method of examination of the heart is of great importance. It has been found to give evidence of myocardial changes in a great variety of disease processes, the acute degenerative changes following coronary thrombosis, the chronic degenerative changes resulting from the gradual narrowing of a single branch or from generalized coronary arteriosclerosis, the acute toxic myocardial changes in diphtheria and typhoid fever, and the inflammatory changes in rheumatic fever and syphilis. The electrocardiographic signs shown in these conditions may be the only discoverable signs of heart disease. Additions and changes have been made in the text to present the important acquisitions of knowledge in the last four years. The most striking change has been the adoption of a new terminology to express the variations of the Q R S group, which Einthoven attributed to hypertrophy of the right or left ventricle. It is believed that when the idea of the electrical axis of the Q R S group is thoroughly grasped the advantages of this conception will be found to be compelling. The mechanical developments of the last few years have given us several new models of the string galvanometer, and satisfactory portable instruments are now available. A new principle of recording the electricity of the heart beat has come into use. The familiar radio amplifier tubes used to increase the power of the heart's current so that a less fragile instrument than the string galvanometer can be used to record the electrocardiogram. These new mechanical features are given sufficient explanatory mention. The ten chapters deal with introductory matter, the normal electrocardiogram and its variations, changes due to hypertrophy of the auricles and ventricles, changes due to myocardial abnormality, clinical significance of abnormal waves, disturbances in rate or rhythm, clinical aspects of abnormal rate and rhythm, clinical application of the electrocardiogram, theory of the electrocardiogram, description and operation of the electrocardiograph, appendices I and II, bibliography and index. The book is well written, the style clear and concise, the ground thoroughly covered, and the illustrations adequate and excellently reproduced. It is an indispensable book to the internist and cardiologist, and will be of the greatest service to the medical student in making clear to him the principles of electrocardiography which he usually finds difficult to grasp.

Recent Advances in Medicine. Clinical Laboratory Therapeutics. By G. E. Beaumont, M.A., D.M.(Oxon.), F.R.C.P., D.P.H.(Lond.), Physician with charge of out-patients, Middlesex Hospital, Physician to the Hospital for Consumption and Diseases of the Chest, Brampton; Medical Tutor and Lecturer in Practical Medicine, Middlesex Hospital Medical School; Sometime Radcliffe Travelling Fellow, University of Oxford; and E. G. Dodds, M.D., Ph.D., B.Sc., M.R.C.P. (Lond.), Professor of Biochemistry in the University of London; Chemical Pathologist to the Middlesex Hospital, Bland-Sutton Institute of Pathology; Pathologist to the Royal National Orthopedic Hospital Fourth Edition. 426 pages and 48 illustrations. P. Blakiston's Son and Co., Philadelphia, 1928. Price in cloth, $3.50.

The four editions of the book have appeared in 1924, 1925, 1926 and 1928. The chief changes in this edition are the introduction of certain methods available in the diagnosis of spinal cord compression from various causes, including an examination of the hydrodynamic and chemical properties of the cerebrospinal fluid by combined cisternal and lumbar puncture and the intrathe-

cal injection of lipiodol. A section has been written on the parathyroid glands including a description of the potent extract recently obtained from them. The theoretical considerations of the action of quinidine have been described much more fully and illustrated by a diagram showing the nature of the circus movement in auricular flutter and fibrillation. The administration of digitalis by cat unit tablets has also been included, and the electrocardiographic changes met with in severe thyrotoxicosis have all been given consideration. The subject matter has been brought up to date by additions and changes in nearly every chapter. This book is a necessity in the clinical laboratory, as it is in some matters ahead of the usual laboratory textbook, and will save literature research. Much valuable information is contained between its covers.

A Handbook of Clinical Gynecology and Obstetrics. By RAE THORNTON LA VAKE, A.B., M.D., F.A.C.S., Assistant Professor of Obstetrics and Gynecology, University of Minnesota; Clinician in Charge of the Obstetric and Gynecologic Department of the University of Minnesota Dispensary. Associate Attending Obstetrician and Gynecologist to the Minneapolis General Hospital. Obstetrician to the Northwestern and Abbott Hospitals, Minneapolis. 281 pages, 35 illustrations. The C. V. Mosby Company, St. Louis, 1928. Price in cloth, $4.00.

This volume is intended for the student, graduate or undergraduate, who is organizing his knowledge of gynecologic and obstetric methods, facts and opinions for practical application. It has evolved out of the demands of instruction given to students in this department during the past twelve years, in conjunction with the demonstration and treatment of cases as they were presented. The first part of the volume presents a cross-section of the problems of a gynecologic and obstetric clinic or office practice with methods of diagnosis and treatment that in the author's experience have stood the test of time and proved themselves the most efficient. The second part aims to give a view of obstetric problems arranged according to their relative importance. The book serves as a special clinic in its presentation of gynecologic and obstetric diagnosis and the problems of therapeusis therewith. An examination of the material of the book shows that it bears out the author's desire to make it practical. It is condensed, well-organized and covers its field very completely. The illustrations are simple line-drawings but indicate sufficiently what they are intended to. It is a useful manual for the student and practitioner.

The Duodenum. Medical, Radiologic and Surgical Studies. By PIERRE DUVAL, JEAN CHARLES ROUX and HENRI BÉCLÈRE of the Surgical Clinic, Faculty of Medicine, Paris. Translated by E. P. Quain, M.D. 212 pages, 127 illustrations. The C. V. Mosby Co., St. Louis, 1928. Price in cloth, $5.00.

The majority of textbook and journal articles dealing with duodenal conditions are responsible for the commonly held opinion that duodenal ulcer is the most important and practically the only pathologic condition of this organ requiring any serious consideration. This book discusses and demonstrates a number of duodenal conditions that have received but slight recognition in medical literature. There are other duodenal conditions, due to congenital disturbances of development, which are equally disabling, nearly as dangerous to life, and perhaps even more common than duodenal ulcer. It is also possible that the cause of certain duodenal ulcers may be found among these lesions. Duodenal obstruction is given a clear and logical interpretation in this volume. The book is compiled by a physician, a surgeon and a radiologist and has required also the assistance of a chemist. This indicates the team-work necessary in the diagnosis of disease of the digestive tract. Such a collaboration is absolutely necessary. The six chapters treat of the duodenum in calculous cholecystitis, essential and stenosing periduodenitis, chronic compression of the third portion of the duodenum by the mesenteric pedicle, duodenojejunostomy, radiologic

signs of ulcer of the duodenal bulb and intoxication in duodenal retention. The illustrations are chiefly radiologic, but are apparently adequate, and are reproduced on glazed paper. The material is far from being a complete discussion of the diseases of the duodenum, and some of the subjects omitted are surprising. For instance, there is practically no mention of duodenal diverticulum and its associated symptomatology and pathology.

Clinical Medicine. By OSCAR BETHEA, M.D., Ph.G., Professor of Therapeutics, Tulane Graduate School of Medicine; Professor of Clinical Therapeutics, Tulane School of Medicine, New Orleans, La. 700 pages, octavo volume. W. B. Saunders Company, Philadelphia and London, 1928. Price in cloth, $7.50.

In this volume the author has attempted to put the most generally accepted information as to the diagnosis and treatment of about one hundred of the most common diseases coming within the province of Internal Medicine. It consists largely of the lectures given by the author to undergraduate and graduate students during recent years at Tulane University. In the preparation of these lectures he has had chiefly in mind the fact that the great majority of patients must be treated in their homes and under conditions offering limited facilities to aid the physician in his efforts. There is no detailed discussion of theory, etiology or pathology; these matters are left to the larger textbooks. The contents are treated under the following heads: respiratory diseases; other specific infectious diseases; diseases of the joints; diseases of the heart; diseases of the kidney and bladder; diseases of the liver, gall-bladder and bile-ducts; gastro-intestinal diseases; diseases of metabolism and nutrition; diseases of the blood; disorders of the nervous system; diseases of the endocrine glands, and a miscellaneous section treating of pellagra, tularemia, epidemic encephalitis and acute anterior poliomyelitis. The book is of the better-grade manual type, and has a good deal of personal experience scattered through it. It is interesting to note that in a book on internal medicine written primarily for New Orleans students there is no mention of yellow fever. The reviewer is not in sympathy with the manual short cut to what is popularly called practical medicine. The separation of therapeutics from a sufficient discussion of etiology and pathology is in his mind a dangerous thing, and does not lead to the best type of medical practice. Unfortunately the average student is only too eager for this sort of thing at the time when he should be cultivating more thorough methods of study and habits of mind.

College News Notes

THIRTEENTH ANNUAL CLINICAL SESSION, BOSTON, APRIL 8-12, 1929
GENERAL CHAIRMAN, DR. J. H. MEANS OF BOSTON
HEADQUARTERS, THE HOTEL STATLER

Preparation for the 1929 Clinical Session

President C. F. Martin and Executive Secretary E. R. Loveland spent some days during the latter part of June in Boston making preliminary arrangements for the next Clinical Session of The College to be held in Boston, April 8-12, 1929. Dr. James H. Means of the Massachusetts General Hospital has been appointed General Chairman of the Session, and is busily engaged in selecting the personnel of the various committees and completing preliminary arrangements for the program. Hospitals and medical institutions generally, in Boston, will co-operate in producing an especially interesting Session.

The new Hotel Statler has been selected for headquarters. It has thirteen hundred rooms, a general assembly hall seating fourteen hundred and equipped with amplifiers so that every member of the audience can hear distinctly, and is equipped with every facility for the handling of a large convention. The technical exhibits will be located throughout the entrance foyer of the assembly hall, providing ideal conditions, not only for the exhibitors, but also for our members examining the new products and devices in the field of internal medicine and associated specialties.

PRESIDENT'S LETTER TO THE COLLEGE

Dear Doctor: In accordance with the practice of former Presidents, I send you my official and personal greetings, and am looking forward with pleasant anticipation to our reunion at the next Annual Meeting, which will take place in Boston, April 8th to 12th, under the auspices of the Harvard Medical School.

Certain changes in the policies and aims of The College now under discussion by the Board of Regents may be of interest.

You are of course aware that the headquarters is permanently located in Philadelphia, and new offices are being acquired this year, where every visiting member will be made welcome.

It has always been the desire of The College to enlist the sympathetic cooperation of as wide and representative a body in the profession as possible, more especially among the men in smaller towns who are trying to practice internal medicine along scientific lines. You may know that our membership has been augmented by twenty-five or more of the most distinguished clinicians in our academic centers, men who are eager and willing to support the efforts of The College in promoting the interests of internal medicine throughout the country.

We have added to our Board of Regents this year Professors J. H. Means of Harvard, J. C. Meakins of Montreal, James Alexander Miller of New York, and James S. McLester of Birmingham, Alabama,—these replacing the members of the Board who have, according to the usual custom, retired.

At a recent meeting of the Board (eighteen members being present), the future policy and plans were fully discussed. It was deemed eminently desirable that the standards of admission should be very clearly defined, and that entrance to The American College of Physicians might be made in every way worthy of the name of our organization.

I take it that the object of The College is chiefly to raise the standards of internal medicine throughout the country. In order to do this we must encourage our prospective members to seek the necessary training and to facilitate as much as possible the means by which this training may be obtained. Your Board feels very strongly that the country is in need of highly qualified, scientific internists, and that by raising the standards of admission we will have taken an important step in bringing about a fulfillment of this need.

Nevertheless it is by no means the feeling of your Board that admission to membership should depend upon research, but rather upon sound training in internal medicine, combined with good character and high ideals. At the next annual meeting a resolution will be placed before the members, proposing to alter the technique of admission of new members to The College. In lieu of the present application form it will be suggested that applicants shall be proposed by two Fellows of the organization, and that even more searching enquiry than heretofore be made as to the fitness of the candidate for admission. Due notice of motion with reference to the contents of this resolution will be mailed to the members.

The subject of initiation fees and annual dues was likewise discussed, and it is the intention of your Board to suggest at the earliest possible moment a radical diminution. Steps have already been taken to consider with special leniency the fees and dues of such members who are on a full-time basis or who are engaged in laboratory work, but the whole subject of the reduction of fees will be considered again at the fall meeting of the Board of Regents prior to the Annual Meeting in Boston.

In conclusion, let me just say that the Regents look forward with very bright hopes to the future of this organization, to the enhancement of its prestige, and to an ever increasing interest in the aims and purposes of our College.

Looking forward to seeing you at our next annual meeting, and with all kind regards,

Believe me,
Very cordially yours,
C. F. MARTIN,
President.

Dr. Allen H. Bunce (Fellow), Atlanta, is Editor of the Journal of the Medical Association of Georgia. Dr. E. C. Thrash (Fellow), Atlanta, is Chairman of the Publication Committee, and Dr. M. M. Head (Fellow), Zebulon, is a member of this Committee.

Those engaged in educational administration and teaching will be interested in an article entitled "An M. D. Degree Five Years after High School," prepared by Dr. Wilburt C. Davison, Dean of the School of Medicine of Duke University. Dr. Davison's paper is reprinted in the June 2, 1928 (pp. 1812-1816) issue of the Journal of the American Medical Association.

Dr. William S. Thayer (Fellow), Baltimore, was a delegate to the Harvey Tercentenary celebration in London during May.

Dr. William R. Dancy (Fellow), Savannah, was made President-Elect of the Medical Association of Georgia at the 79th Session of the Association at Savannah, May 9-11. Dr. William A. Mulherin (Fellow), Augusta, retired as President of the Association at this session.

Dr. David Riesman (Fellow), Philadelphia, has been made a Knight of the Order of the Crown of Italy. Dr. Riesman is Professor of Clinical Medicine at the University of Pennsylvania School of Medicine.

Dr. Thomas R. Brown (Fellow), Baltimore, has been re-elected President of the Johns Hopkins Medical Alumni Association.

Through Dean Russell H. Oppenheimer (Fellow), Emory University, at Atlanta, Georgia, has arranged Alumni Medical Clinics, beginning June 4 and ending June 8. Several Fellows of The College appear on the program to give clinics on various topics in the field of Internal Medicine.

Dr. Ellis Lamb (Fellow), Clinton, Oklahoma, is President-Elect of the Oklahoma State Medical Association.

Dr. L. B. McBrayer (Fellow), Southern Pines, was re-elected Secretary of the Medical Society of the State of North Carolina at its annual meeting at Pinehurst, April 30-May 2.

The National Board of Medical Examiners will hold examinations in parts I and II, September 12-14. Between the time the divided examination was established by the Board in 1922 and March 31, 1927, candidates for examination from Harvard Medical School exceeded the number from any other institution. Pennsylvania was second, Johns Hopkins, third, Rush, fourth, and Columbia, fifth. Two hundred and seventy-two physicians completed qualifications during 1927.

Dr. Edward B. Krumbhaar (Fellow), professor of Pathology in the University of Pennsylvania School of Medicine, has been elected President of the American Association of Pathologists and Bacteriologists and also President of the American Society of Experimental Pathology.

Dr. Thomas P. Murcock (Fellow), Meriden, Conn., was elected President of the New Haven County Medical Society for the current year.

Dr. Edward Francis of the United States Public Health Service and Dr. Walter M. Simpson of the Miami Valley Hospital, Dayton, Ohio, were each awarded a Gold Medal for their important work on Tularemia, as shown in their exhibits in the Scientific Exhibit of the American Medical Association at the Minneapolis Meeting. Dr. Simpson's article in the June number, an abstract of which was presented at the New Orleans Clinical Week, has attracted much attention.

Dr. Robert Oden (Associate) of Washington, D.C., was recently honored by the King of Sweden with the bestowal of the Order of the Commander of Vasa. In 1920, Dr. Oden was also honored by the Swedish King with the Knight of the North Star, in recognition of his research work in medicine.

Dr. Oden was born in Sweden but is now a citizen of the United States. He is a graduate of the George Washington Medical School and pursued postgraduate study at Johns Hopkins, and at various clinics in London, Paris, Berlin and Vienna.

Dr. W. S. Leathers (Fellow), Nashville, Tenn., was re-elected a member of the National Board of Medical Examiners at Washington on May 3.

Under the title of "Problem of Indian Administration," the Institute for Government Research has published a report of a two years' survey of conditions in the Indian Territory, made at the request of the Secretary of the Interior, Dr. Hubert Work (Fellow). The report covers the prevalence of certain diseases among the Indians, the conditions of living, the medical and hospital service offered, the health administration work of the Government, etc.

Dr. James S. McLester (Fellow), Birmingham, was recently elected a member of the Board of Censors of the Alabama State Medical Association.

Dr. J. Birney Guthrie (Fellow), New Orleans, was elected Vice President of the Louisiana State Medical Society at its recent meeting held in Baton Rouge.

The May issue of the Journal of the Tennessee State Medical Association carries four major articles by Fellows of The College:

"The Liver," by Stewart R. Roberts, Atlanta, Georgia.

"Heart Failure," by J. O. Manier, Nashville, Tennessee.

"Periodic Health Examinations," by E. R. Zemp, Knoxville, Tennessee.

"Classification of the Anemias and Discussion of the Most Important Types," by William C. Colbert, Memphis, Tennessee.

Sir Humphrey Rolleston, Regius Professor of Physic, University of Cambridge, England, delivered on March 20-21, the first course of lectures at Johns Hopkins University under the William Sydney Thayer (Fellow) and Susan Read Thayer, Lectureship in Clinical Medicine. This lectureship was endowed by friends of Dr. Thayer last year when the American Medical Association met in Washington and made Dr. Thayer President-Elect of that organization.

At the Minneapolis Session of The American Medical Association, diagnostic clinics were conducted by the following Fellows of The College on June 11:

Dr. W. McKim Marriot, St. Paul, "Pediatrics";

Dr. F. M. Pottenger, Monrovia, "Pulmonary Tuberculosis and Bronchiectasis";

Dr. Elliott P. Joslin, Boston, "Diabetes";

Dr. John H. Musser, New Orleans, "Pernicious Anemia."

Dr. Charles A. Reye (Fellow), Charleston, is President of the West Virginia State Medical Association.

Dr. Edward J. G. Beardsley (Fellow), Philadelphia, recently addressed the Ohio County Medical Society, Wheeling, West Virginia, on "Conditions that Simulate Pneumonia."

Dr. David Riesman (Fellow), of Philadelphia, was awarded the degree of Doctor of Science at the commencement exercises of Franklin and Marshall College at Lancaster, Pa., on June 5.

Dr. Waller S. Leathers (Fellow), Nashville, Professor of Preventive Medicine and Associate Dean of the Medical School of Vanderbilt University, was appointed Dean of said school by the Board of Trustees of that institution at their meeting on June 12. Dr. Leathers succeeds Dr. G. Canby Robinson who recently resigned to become Director of the medical center of Cornell University and the New York Hospital in New York City. Dr. Leathers was formerly Dean of the Medical School of the University of Mississippi and Executive Officer of the State Board of Health.

Harvard University at its annual Commencement on June 21, conferred the Honorary Degree of Doctor of Science on Dr. George R. Minot (Fellow), of Boston.

Dr. Hubert Work (Fellow), Secretary of the Interior in the Cabinet of President Coolidge, has been appointed Chairman of the Republican National Committee, which will manage the campaign of Secretary Hoover and Senator Curtis, the Presidential and Vice-Presidential nominees. Dr. Work announced that he would retire as a member of the Coolidge Cabinet.

Dr. James M. Anders (Master), of Philadelphia, was honored by the Degree of Doctor of Science at the Commencement Exercises of the University of Pennsylvania.

OBITUARY

"Valdemar Sillo, M.D., of 353 West 57th Street, New York, N. Y., was born in 1867 and graduated as physician from the Eclectic Medical College in the City of New York in 1902. He practiced medicine in the City of New York and was well liked by his patients and colleagues. He was an honest straightforward man, a competent physician and a true friend. Goiter and angina pectoris carried him off from this world on October 29th, 1927.

"We express our sympathy to the widow and the near relatives. Dr. Valdemar Sillo will live in the memory of his friends as an example of good fellowship."

YEAR BOOK SUPPLEMENT

The Executive Offices are busily engaged in preparing the 1928 Supplement to the 1927-28 Year Book of The College. It will be remembered that the Board of Regents determined upon the policy of printing a Year Book only every second year and to print a Supplement, during the intervening years, of the new elections to membership. The 1928 Supplement went to press July 1 and will be distributed about September 1.

1928 MEMBERSHIP DUES

The Executive Offices report that there are a number of members who have delayed payment of the 1928 dues and that, in consequence, their names cannot be entered on the subscription list to receive Volume II of Annals of Internal Medicine. It is hoped that all such delinquent members will promptly attend to the payment of their dues. Members delinquent in dues two years may be automatically dropped from the roll of The College.